Non-Invasive Monitoring of Human Health Using Eye as a Window to the Body

Medicine Beyond Tomorrow: Early Detection & Prevention

Rafat R. Ansari, Ph.D.

2009 NASA Occupational Health Meeting

Investigators and Collaborators:

Manuel B. Datiles, MD, NEI/NIH (Clinical studies of early onset of oxidative stress leading to cataract)

James S. Logan, MD, NASA JSC (Diver study)

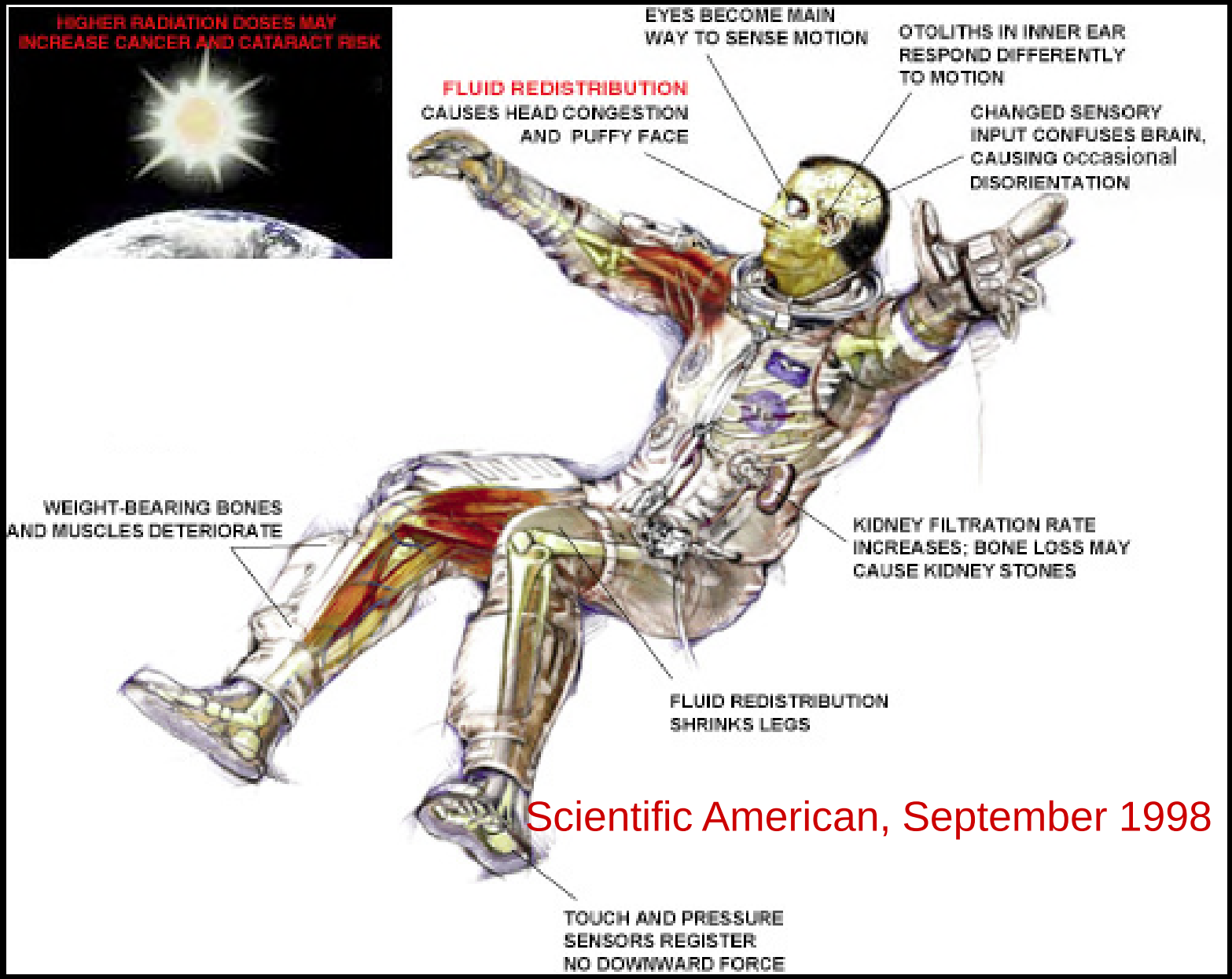
Jeffery A. Jones, MD, NASA JSC (Early onset of oxidative stress in flight crews and blood perfusion studies in fingertips)

Christopher Blasio, CIS, CHP, NASA GRC (Laser safety calculations for IRB's and CPHS process)

James F. King, NASA GRC (Engineering support)

ABC NEWS HOUSTON

Space Travel: Serious Health Risks!



Scientific American, September 1998

Potential Ocular Risk Factors in Space Flight

Cataract, Increased IOP, Decreased Visual Acuity, Conjunctivitis, Photopsia, Macular Degeneration/Nutrition

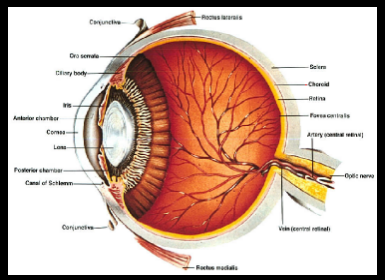
R.R. Ansari and J. Sebag in Teleophthalmology, Springer-Verlag, 2006

In the absence of proper countermeasures space travel accelerates the aging process

Our Objective

Diagnose diseases non-invasively long before the clinical symptoms appear and help find non-surgical countermeasures

Looking at the Molecular Level



"Window to the Soul", could it be a "Window to the Body"?

EYE "MICROCOSM OF THE BODY"

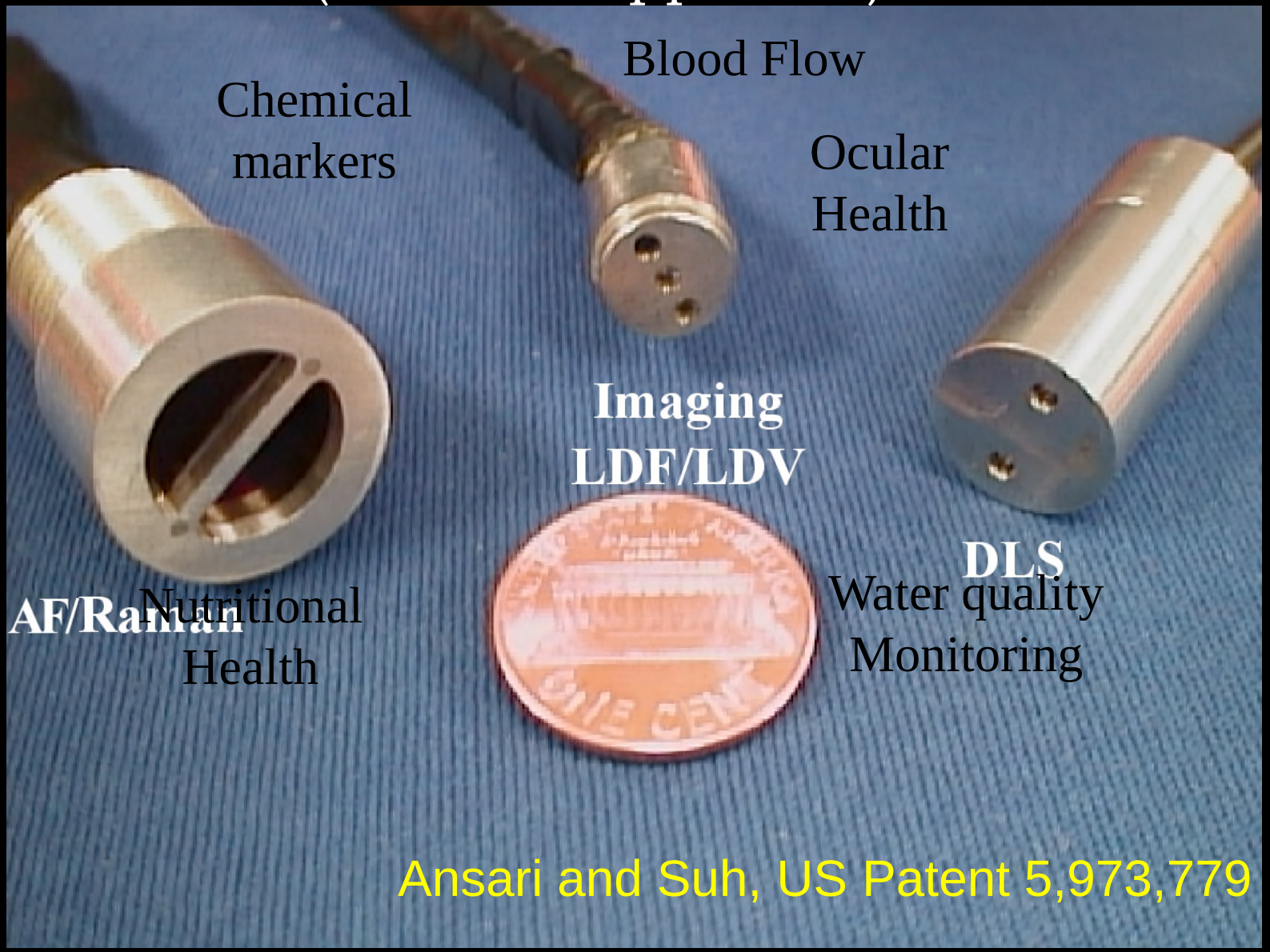
- Eye is built like a camera.
- Light from cornea to the retina traverses through tissues that are representative of nearly every tissue type in the body.
- **Cornea:** typical extra-cellular matrix composed primarily of collagen.
- **Aqueous:** an ultrafiltrate of blood, containing most of the molecules found in serum at concentrations that are reflective of serum levels.
- **Lens:** highly organized array of crystallin proteins.
- **Vitreous:** similar in nature to the articular cartilage and synovial fluid found in joints.
- **Retina and optic nerves** are in fact part of the central nervous system.
- Since eye is easily accessed by light, the optical technologies can be used for the evaluation of structure and physiology in health, aging, and disease.

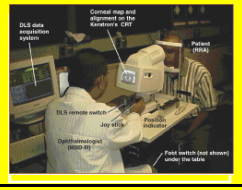
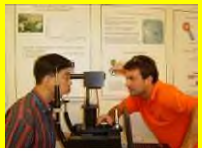
Requires Development of Compact, Low-Power, Light-weight, Sensitive, Non-Invasive Technologies

Looking at the Molecular Level

Non-Invasive Compact Fiber Optic Probes

(Modular approach)

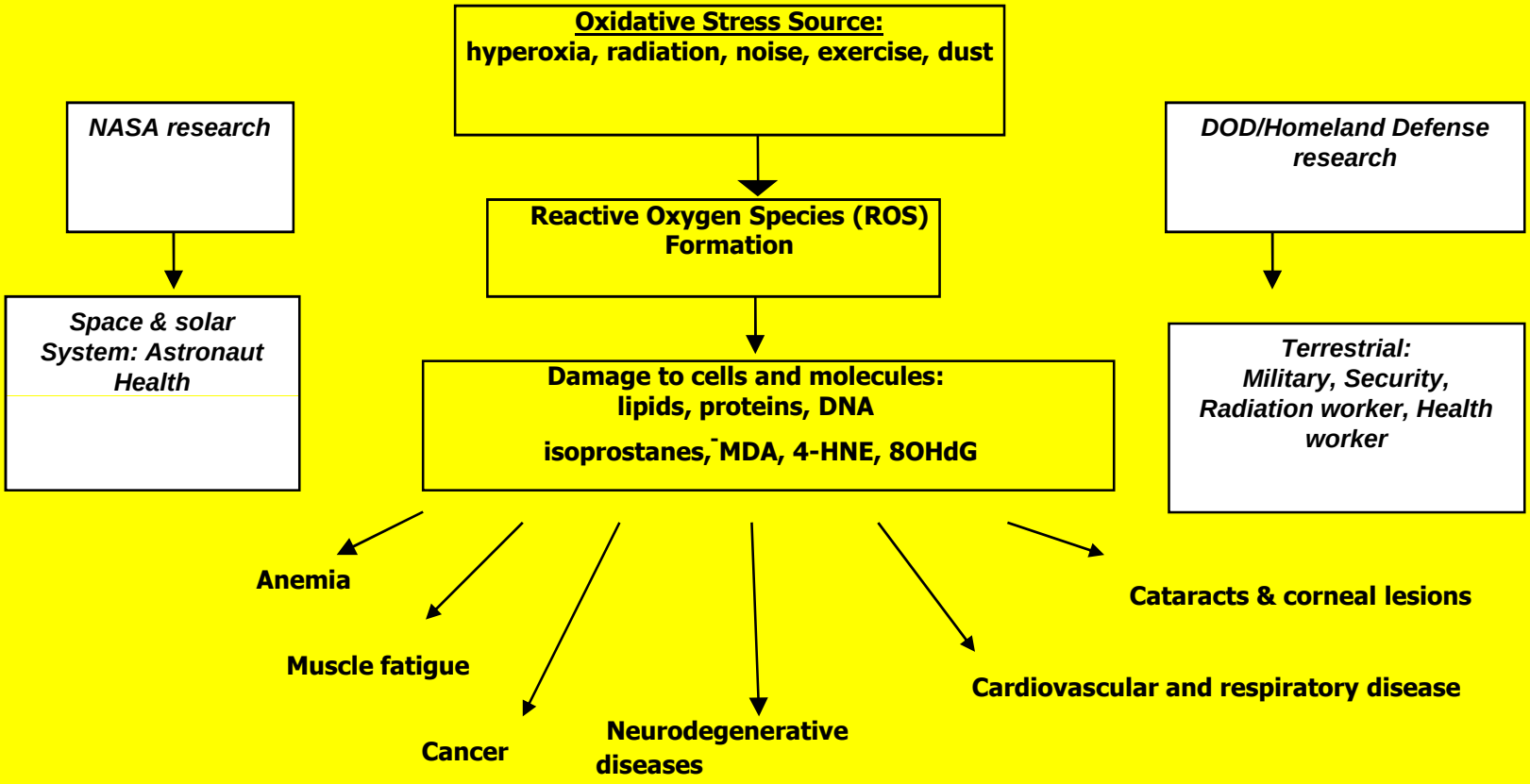


Technologies and Readiness Level	Instruments in Use	Diseases/Studies
Dynamic Light Scattering (DLS) In Clinical Use		Corneal Diseases and Wound Healing (LASIK), Lens Aging and Cataract, Uveitis, Glaucoma, Vitreous Aging and Lysis Studies, Drug Efficacy Studies, Alzheimer's, Cholestrol, Studies on Effects of Radiation, Hyperbaric Oxygen and other conditions on Eye Tissues, Diabetic Vitreopathy
Corneal/Lens Autofluoresence Some Clinical Data		• Radiation induced biological effects • Diabetic Retinopathy
Laser-Doppler Flowmetry (LDF) (Flown on KC-135) In Use JSC Astronaut Suit Lab		• Physiological circulatory changes • Hemodynamic Response/Fingertip Study • Choroidal blood circulation • Age-related Macular Degeneration (AMD) • Diabetic Retinopathy
Raman Carotenoid Dispersion Analysis In Clinical Use		• Lack of Nutrition (Luetin/Xeaxanthin) • AMD • Skin cancer • Stress status of living plants and plant products
Ocular Polarimetry (optical activity) Laboratory Use		• Blood-glucose Sensing 
Tissue Oximetry (Flown on KC-135 and Single-Engine Airplane		• Muscle Atrophy and Osteoporosis • Hyper-/Hypo-tension •Functional Imaging of Brain • Occult Blood Loss • Pilot Fatigue/Flicker Study
Tissue Capillaroscopy (In Design Stage for use in Conjunctiva)		• Micro-circulation/Blood vessel tortuosity (long-duration confinement/bed rest/exercise, Immune system) • Functional Imaging of Blood Flow
Celestial and Terrestrial Tele-Ophthalmology: All of the above in a Tele-medicine Integrated Head-mounted Goggle-like Diagnostic Device **(**Under Development)		• Various Ocular and Systemic diseases using "Eye as a window to the body" ***NEW TECHNOLOGIES***

Current Studies

Ocular Diseases:	Cataract, AMD
Systemic Diseases:	Alzheimer's, Diabetes
Space Medicine Issues:	Radiation effects, EVA's (finger-tip injuries)
Occupational Medicine:	Oxidative stress in JSC diver population
Aviation Medicine and Safety:	Pilot Fatigue & neurovestibular effects (Flicker Vertigo)

Oxidative Stress Leads to Aging and Disease



Whole body cellular level injuries occur with oxidative stress due to reactive oxygen species (ROS)

Diseases of radiation-exposed tissues linked to Oxidative Stress

- Cataracts (Space and Aviation Crews)
- Age-Related Macular Degeneration

Cosmic Radiation Increases the Risk of Nuclear Cataract in Airline Pilots

Vilhjalmur Rafnsson etal, Arch Ophthalmol. 2005;123:1102-1105

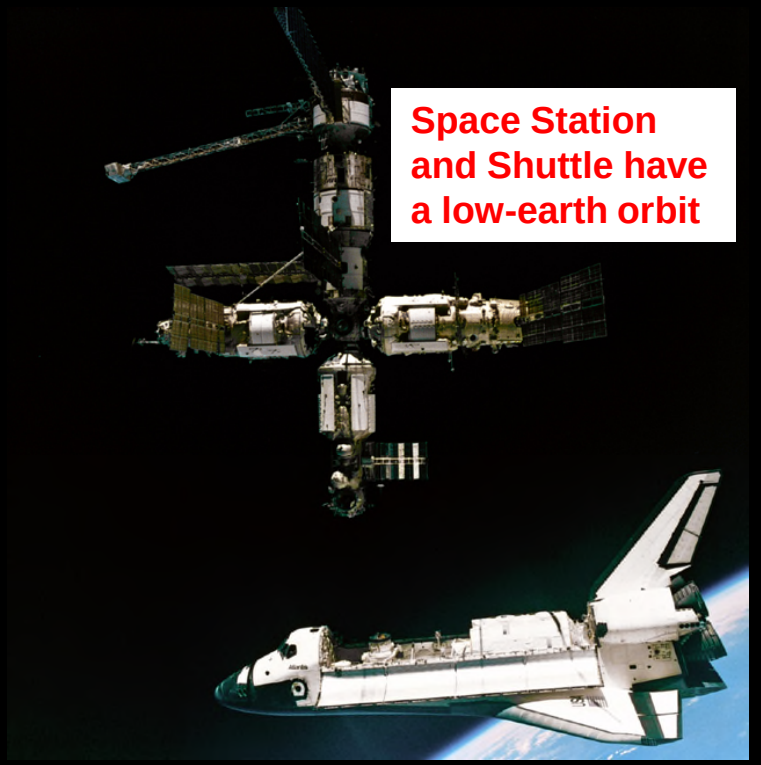
Population-based case-control study of 445 men.

Conclusion: The association between the cosmic radiation exposure of pilots and the risk of nuclear cataracts, adjusted for age, smoking status, and sunbathing habits, indicates that cosmic radiation may be a causative factor in nuclear cataracts among commercial airline pilots.

NOTE: 0.5 REM/year compared with 5 REM/year for the Radiation worker

295 Astronauts longitudinal study at NASA JSC

Relatively low doses of space radiation are causative of an increased incidence and early appearance of cataracts



Space Station and Shuttle have a low-earth orbit

Cucinotta et al., “Space radiation and cataracts in astronauts”, Radiation Research, Vol.156, No. 5, 460-466, Nov. 2001.

Rastegar et al., “Radiation Induced cataract in astronauts and Cosmonauts”, Grae. Arch. Clin. Exp. Oph., 240 (7) 545, 2002.

Global Blindness

- 37 million blind people and 124 million with low vision, excluding those with uncorrected refractive errors.
- The main causes of global blindness are cataract, glaucoma, corneal scarring (from a variety of causes), age-related macular degeneration, and diabetic retinopathy.
- Global Vision 2020 initiative is having an impact to reduce avoidable blindness particularly from ocular infections, but more needs to be done to address cataract, glaucoma, and diabetic retinopathy.

A Foster and S Resnikoff, “The impact of Vision 2020 on global Blindness”, Eye (2005) 19, 1133–1135.

BLINDNESS: A Global Tragedy

Seeing-eye Children of Africa

Photo taken from LIFE Magazine Aug 94 issue.

LIFE August 1994

Problems due to Aging here on Earth

BLINDNESS DUE TO CATARACTS

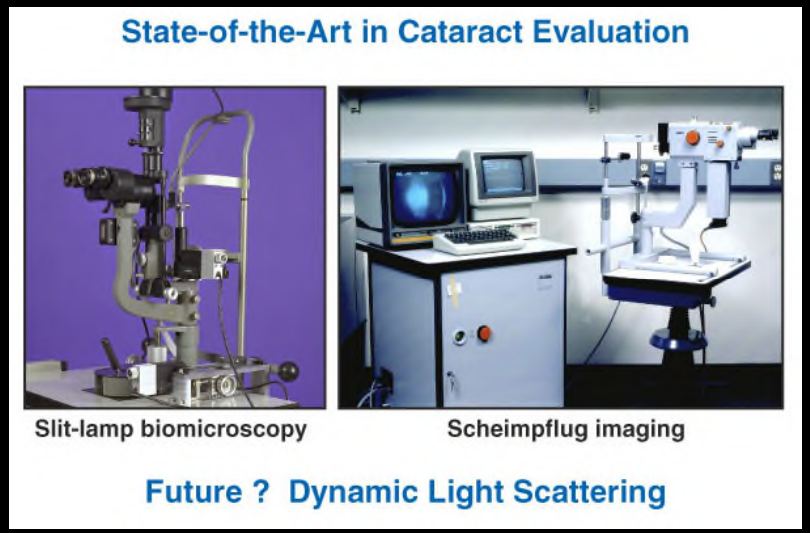
- Worldwide, 50% of all blindness is due to cataracts
- No medical treatment
- 1.4 million cataract surgeries are performed each year in the U.S.
- $3.4 billion spent through Medicare
- 34 million Americans have cataracts over the age 65
- 70 million Americans will have cataracts in year 2030 compared to 34 million figure today

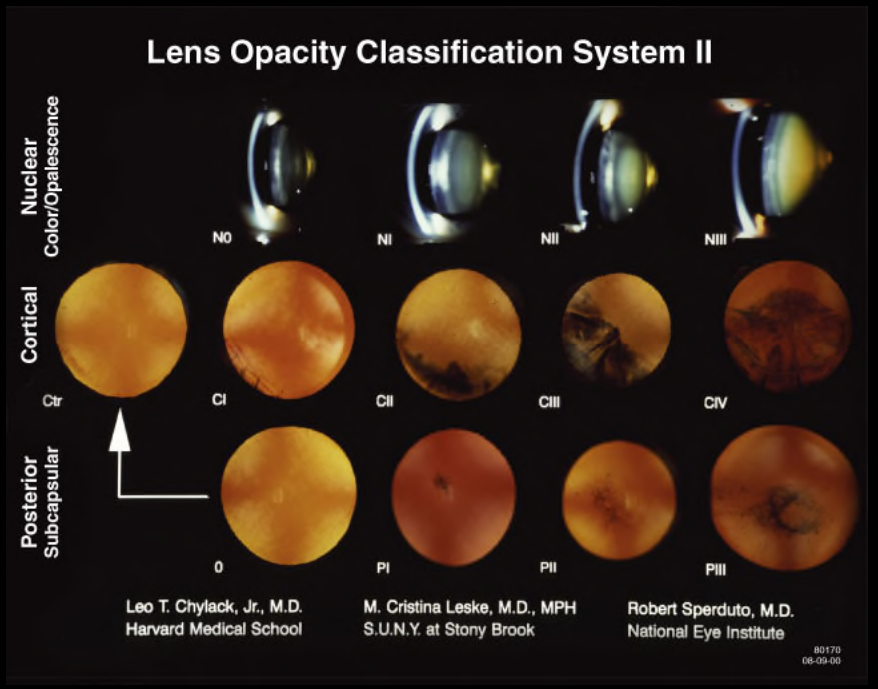
"A delay in cataract formation of about 10 years would reduce the prevalence of visually disabling cataract by about 45%"

(Carl Kupfer, MD, Director NEI/NIH, The Conquest of Cataract: A Global Challenge, trans. Ophthal., Soc., UK, 1985)

PRESENTLY CATARACT DIAGNOSIS IS BASED ON PHOTOGRAPHIC IMAGING

Qualitative and not an Early Measure of Cataractogenesis





DLS is 2-3 orders of magnitude more sensitive

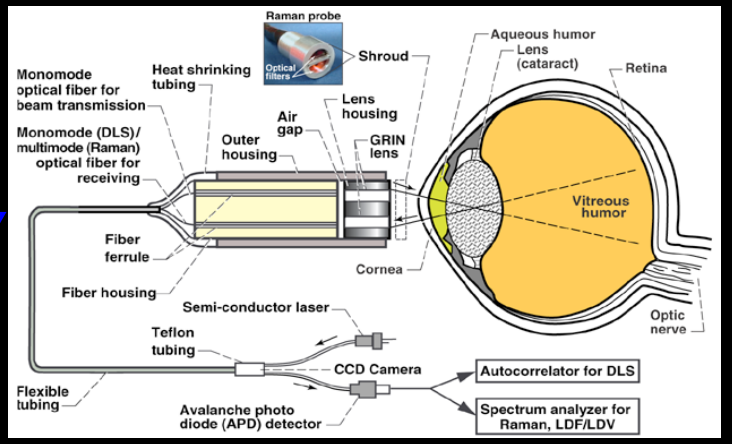
Datiles and Ansari, Chapter 73B, Duanne's Clinical Ophthalmology, 2009

Dynamic Light Scattering

Quasi-Elastic Light Scattering

Photon-Correlation Spectroscopy

New Developments and Use in Ophthalmology



Ansari, R.R., "Ocular Static and Dynamic Light Scattering: A Non-Invasive Diagnostic Tool for Eye Research and Clinical Practice", J. Biomed. Optics, 9(**1**) 22-37, 2004.

Ansari, R.R., "Quasi-Elastic Light Scattering in Ophthalmology", *Coherent-Domain Optical Methods for Biomedical Diagnostics, Environmental and Material Science*, Kluwer Academic Presss, Chapter 11, 2004.

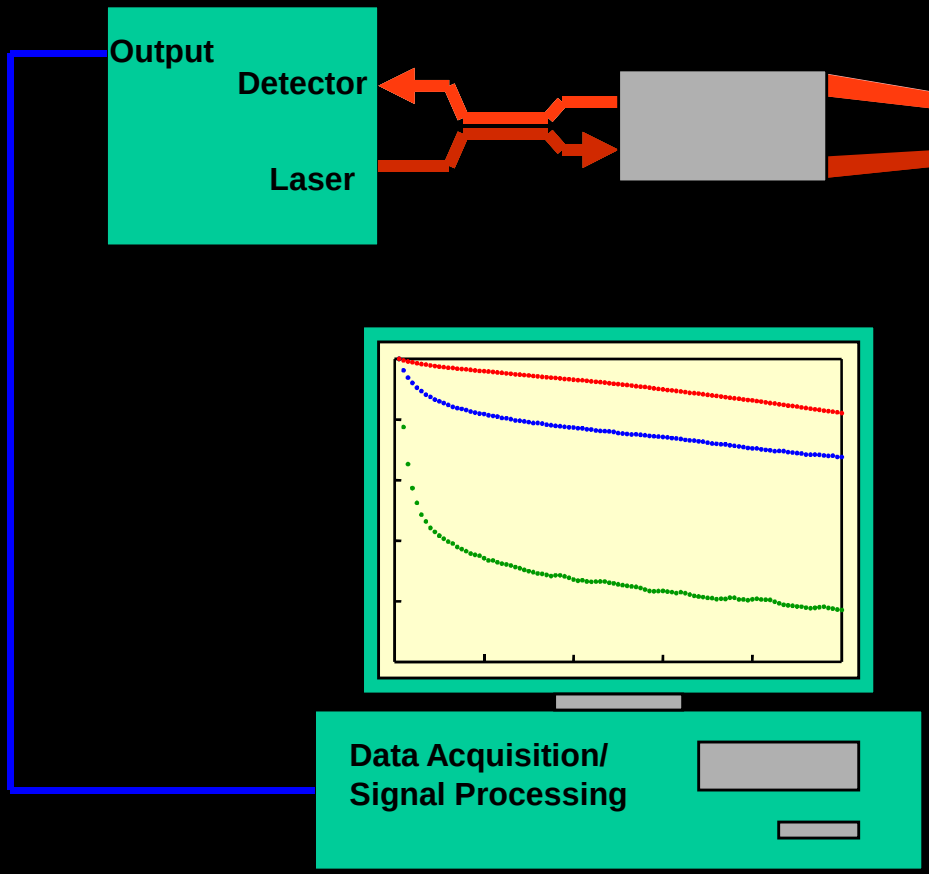
Recent Studies on oxidative stress

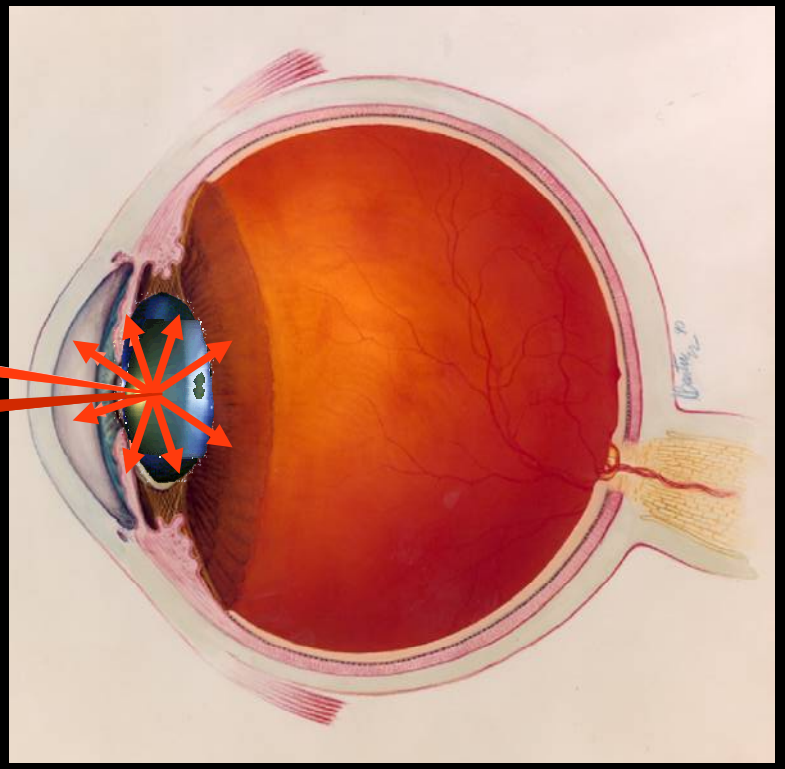
- *Aging Baseline established (humans)*
- *Response to HBO established (guineapigs)*
- *Response to UVB established (guineapigs)*
- *Response to ionizing radiation (rabbits)*
- *Response to anti-oxidant treatment to treat cataract (rats)*

UV Radiation Environment: J. Photochemistry and Photobiology, November 2008

Hyperbaric Oxygen Environment: IOVS, Vol. 46, No. 12, pp 4641-4651, December 2005.

How the Early DLS Detection System Works?

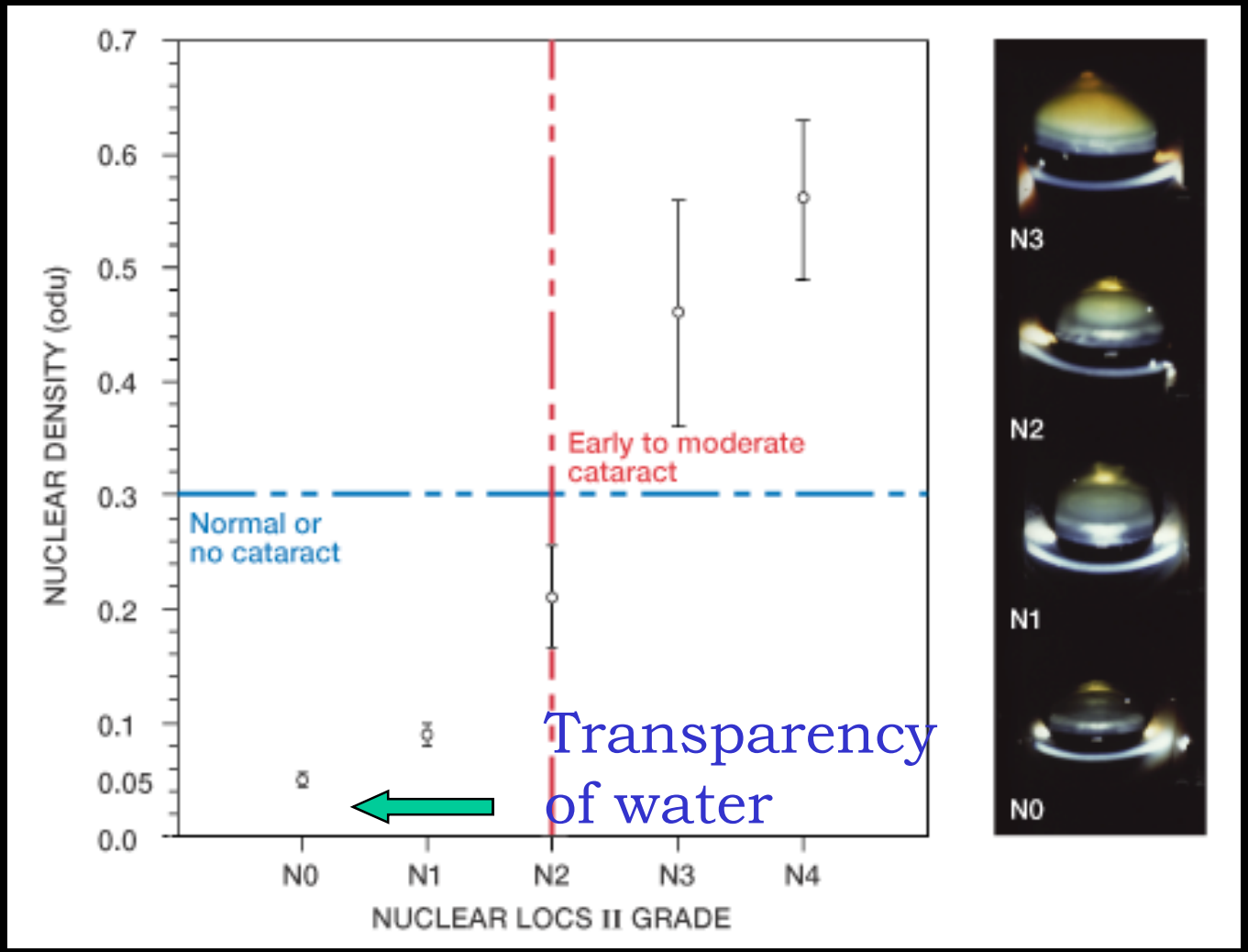




Laser Power: 100 Micro Watts
Exposure Time: 5 Seconds

Datiles and Ansari, “Evaluation of Cataracts”, in Duannes Clinical Ophthalmology, Chapter 73-B, Lippincot Williams Wilkins, 2004

Association Between Nuclear Opalescence LOCS II Grades Obtained Clinically and the Nuclear Densities (odu), Together With 95% Error Bars

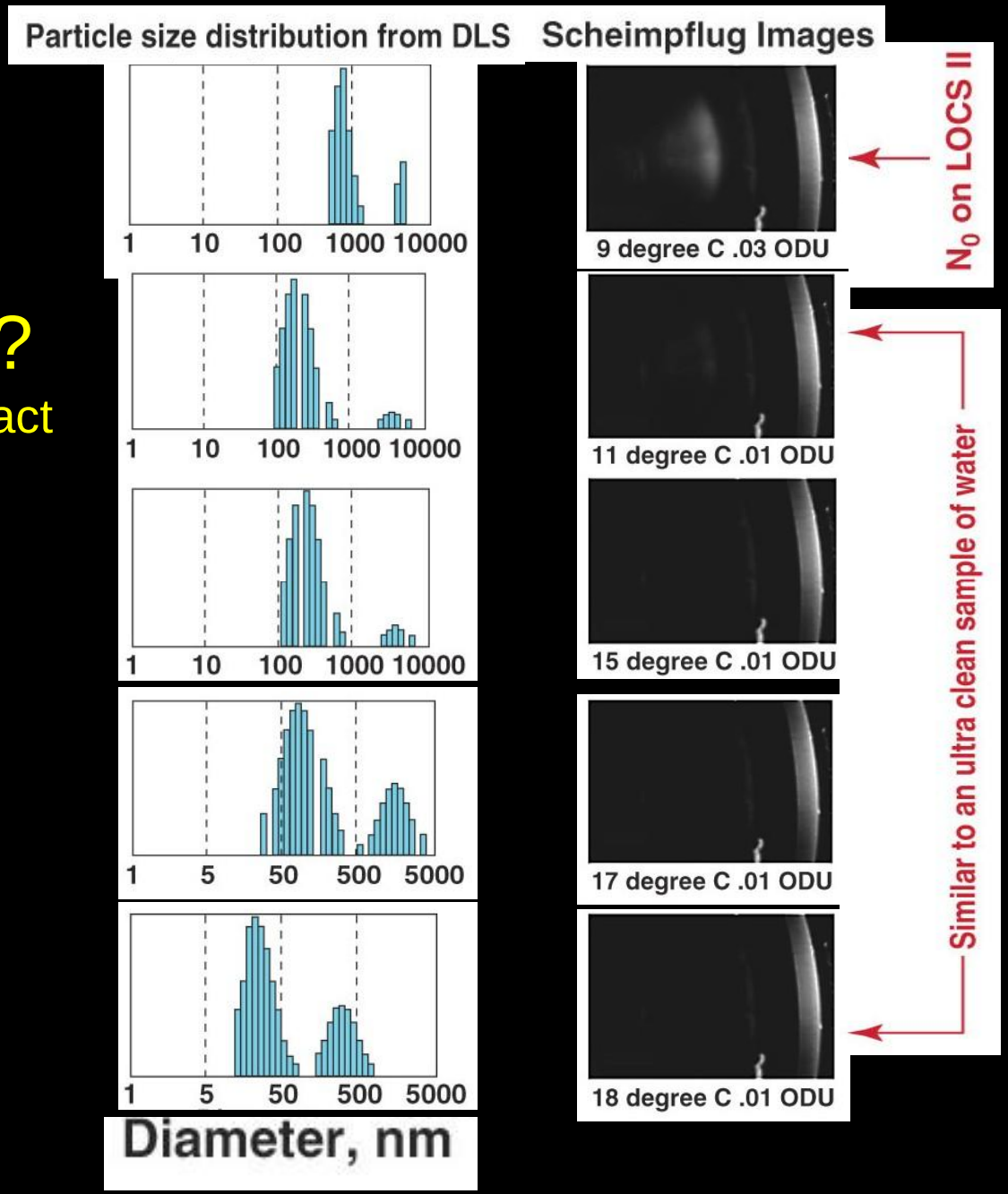


Datiles, M. et. al, Brit J. Ophthalmol. Vol. 79, 527-534, 1995

Sensitivity of DLS compared To Scheimpflug?

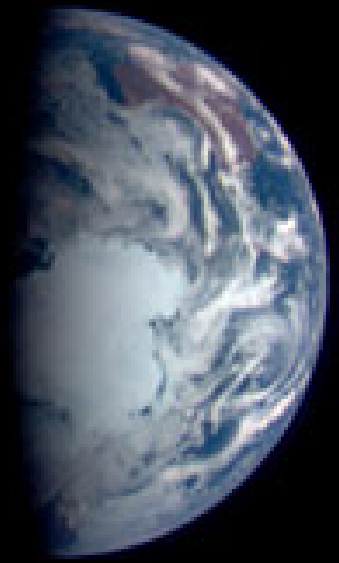
(in a Cold-Induced Cataract Model; Intact Calf Eyes)

Ansari and Datiles, Exp. Eye Res., Vol. 74, 93-102, 2002



Evaluation of Pre-senile Cataract with DLS and Comparison with AREDS Optical Lens Grading System

NASA-NEI Collaboration



Manuel Datiles, MD

Rick Ferris, MD

George Reed, PhD

Susan Vitale, PhD

Kwang Suh, PhD

Rafat Ansari, PhD

Recent Clinical Study:

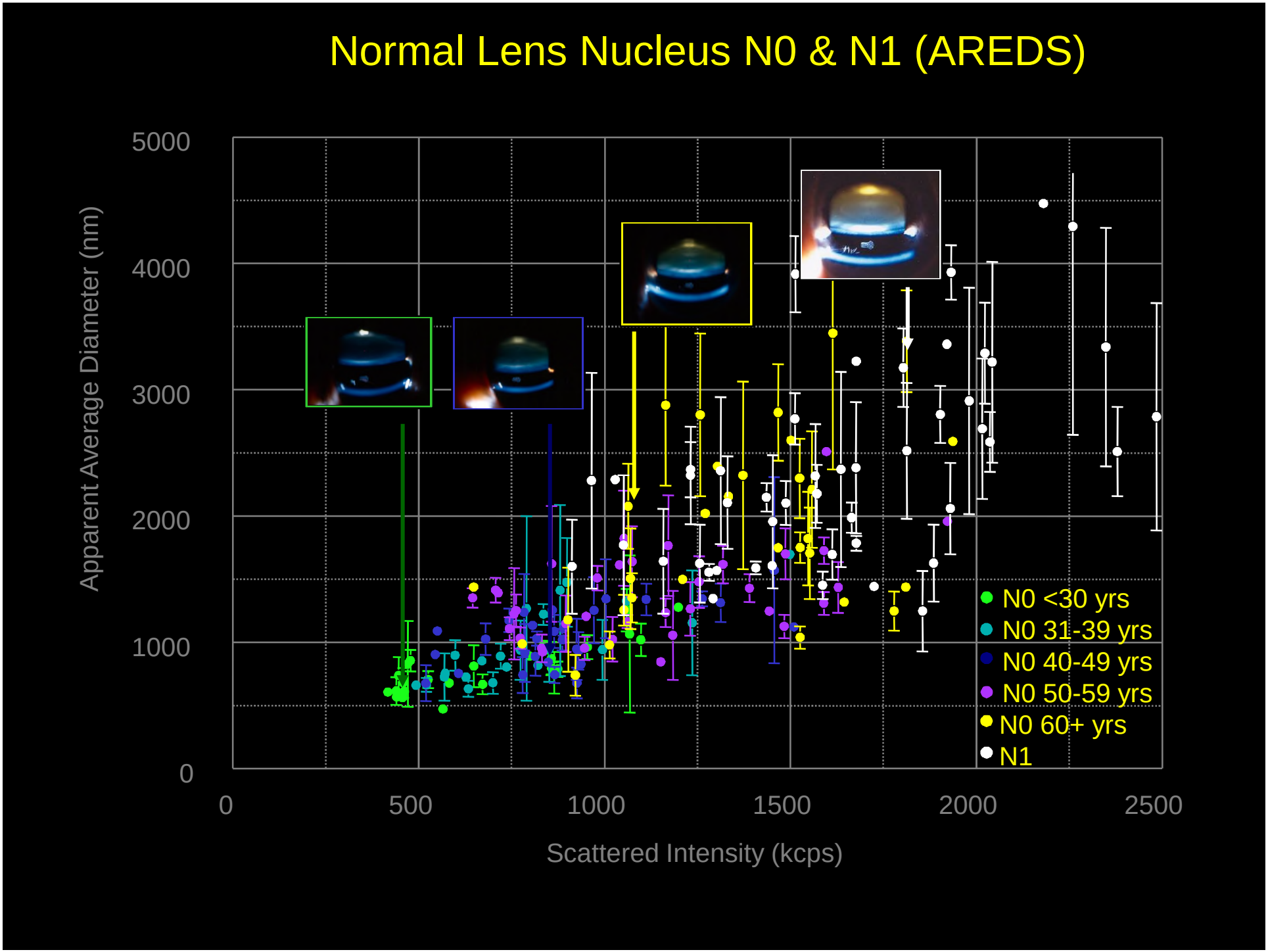
***Alpha-Crystallin Index:* A New Parameter to Assess Susceptibilty to Oxidative Stress leading to Cataract in Humans using DLS**

Archives of Ophthalmology Vol. 126, December 2008

NASA's Clinical DLS Device in use at NEI/NIH (M.B. Datiles III, M.D.)

DLS Probe Mounted on a Keratron for Lens and Cornea

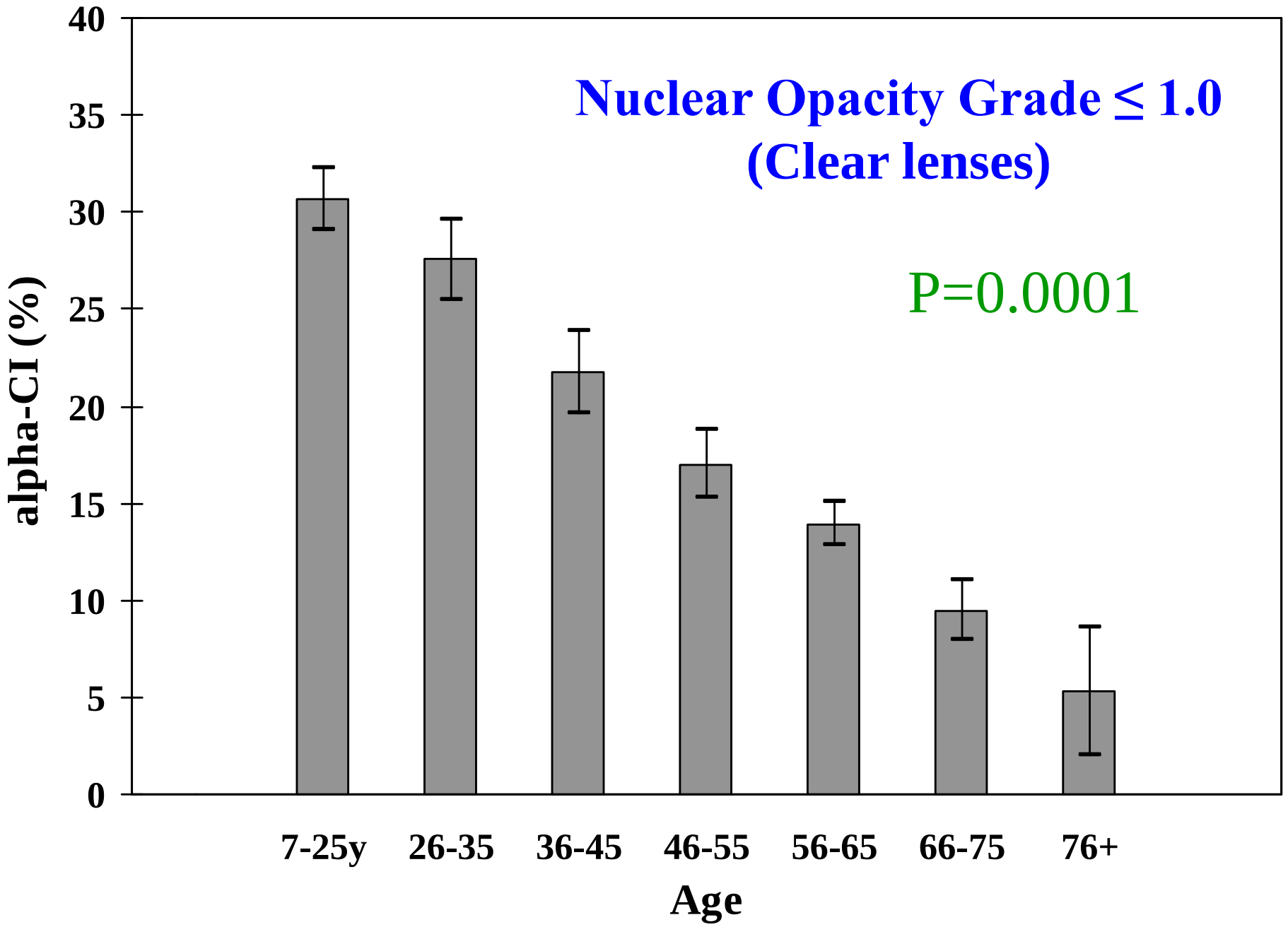
Normal Lens Nucleus N0 & N1 (AREDS)

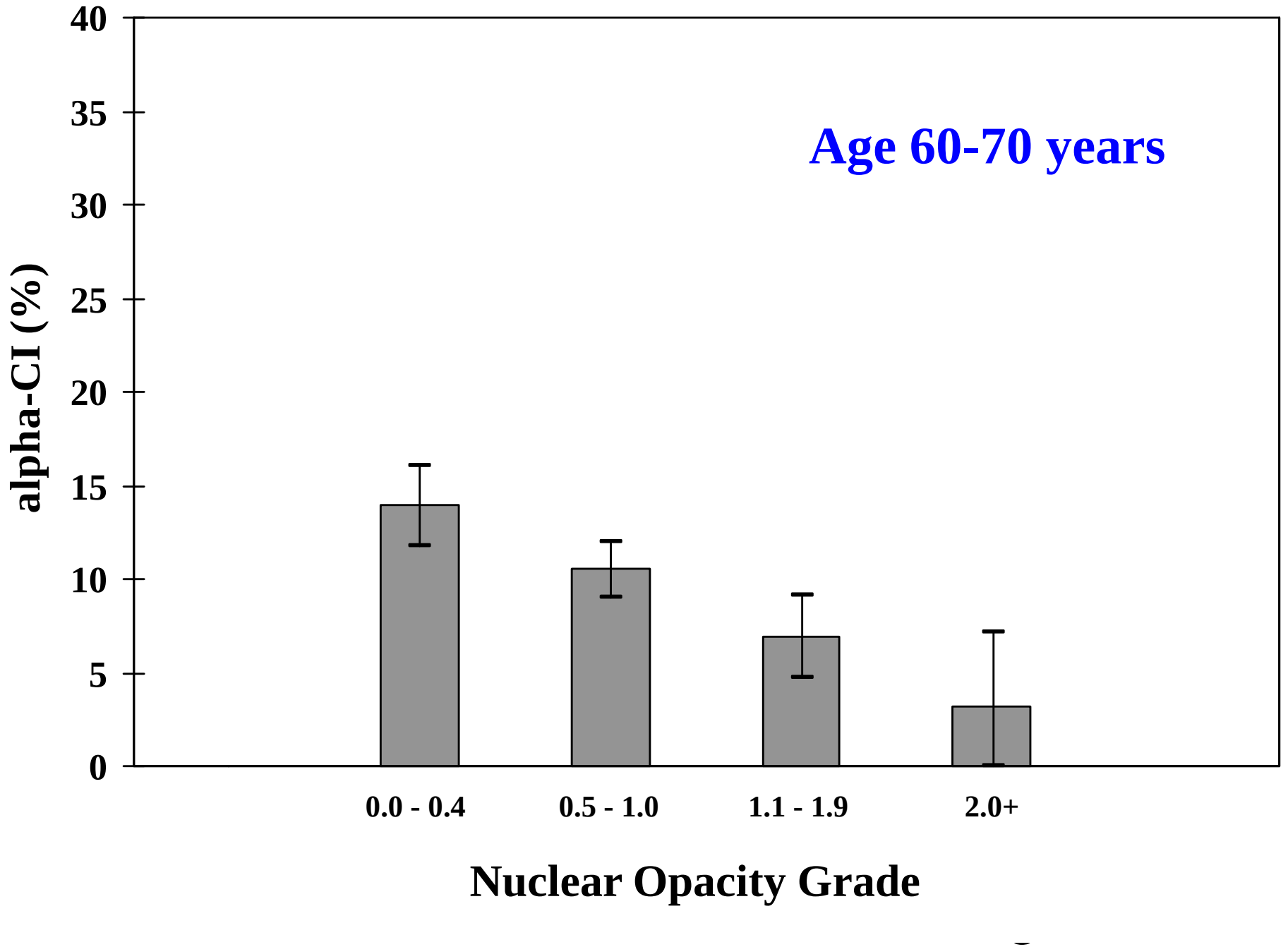


DLS Size Distribution (Age/AREDS)

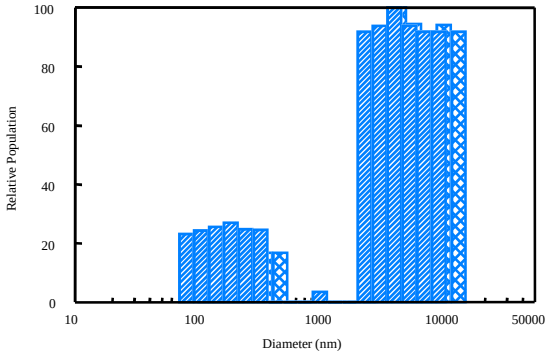
The α -Crystallin Index: a new parameter to assess oxidative stress and susceptibility to Cataract

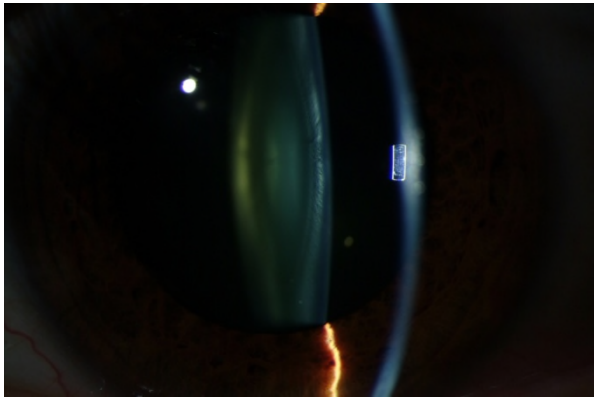
- α Index: Amount of unbound alpha-crystallin in the lens.
- Act as molecular chaperones which prevent lens protein aggregation due to oxidative stress
- Decreasing levels of alpha-crystallin are associated with increased risk of nuclear sclerosis


Nuclear Opacity Grade ≤ 1.0
(Clear lenses)
P=0.0001
alpha-CI (%)
40
35
30
25
20
15
10
5
0
7-25y
26-35
36-45
46-55
56-65
66-75
76+
Age

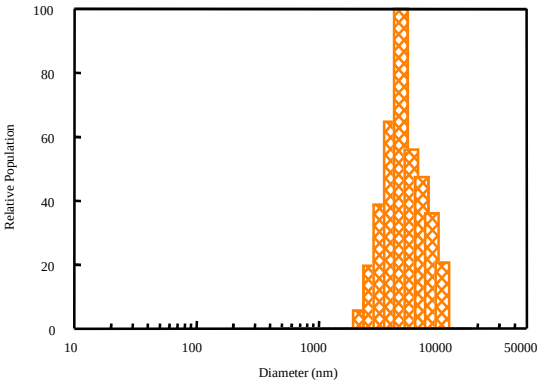

Age 60-70 years
alpha-CI (%)
40
35
30
25
20
15
10
5
0
0.0 - 0.4
0.5 - 1.0
1.1 - 1.9
2.0+
Nuclear Opacity Grade

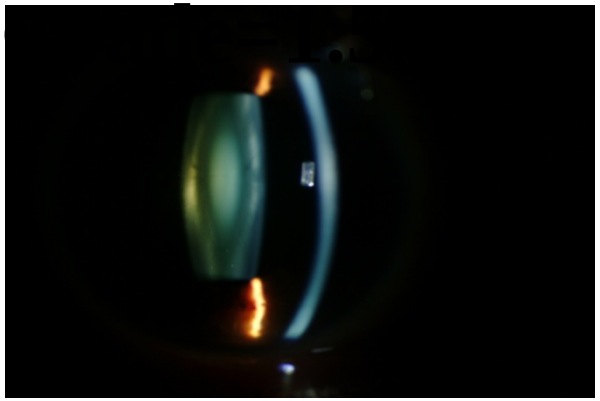
11 month Follow up of Pre-Senile Nuclear Cataract





AREDS Nucleus



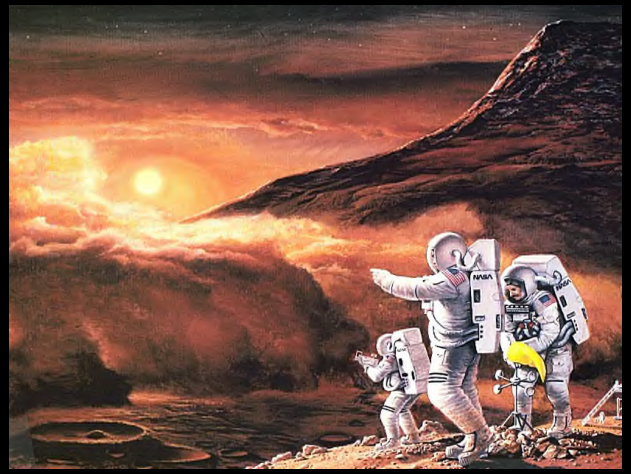


AREDS Nucleus Grade=2.5

Conclusions and Current Status

- The αCI, a measure of the amount of alpha-crystallin in the lens significantly decreases with age and with cataract formation.
- Decreasing levels of α-crystallin are associated with increased risk of Oxidative stress.
- Currently, clinical work is continuing at NIH and Wilmer Eye Institute of Johns Hopkins- Oxidative Stress Mechanism post vitrectomy surgeries- synergistic with DARPA/NASA proposed work.

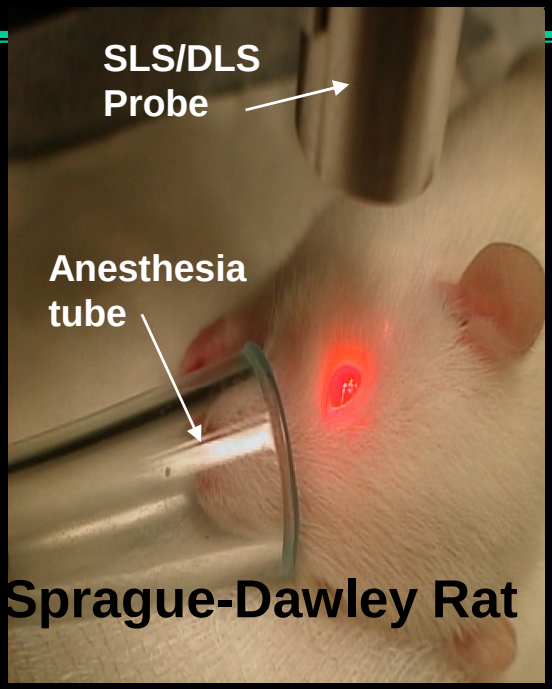
Cataract Prevention or Reversal ?



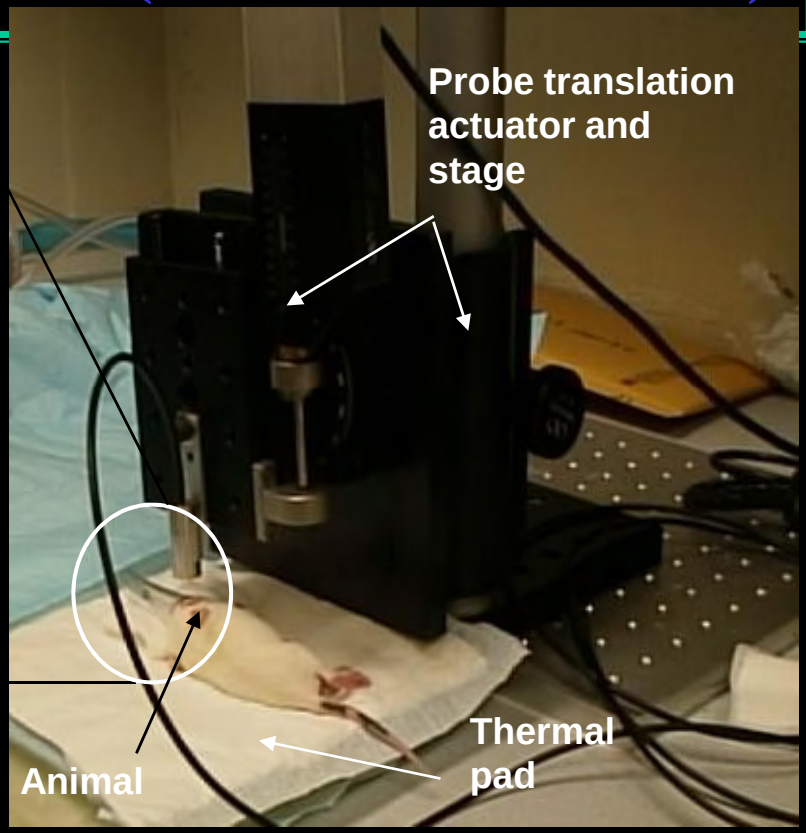
Is Treatment Possible ?

- Aldose Reductase Inhibitors
- Pantethine
- Tempol-H (NIH)
- Antioxidants (red wine, tea caretonoids, isoflavones)
- Vitamin Supplements (AREDS Study)

Countermeasures
Cataract Treatment in Rats (33 Animals Studied)



Animal Close-up



Measurement Time: 5 Sec

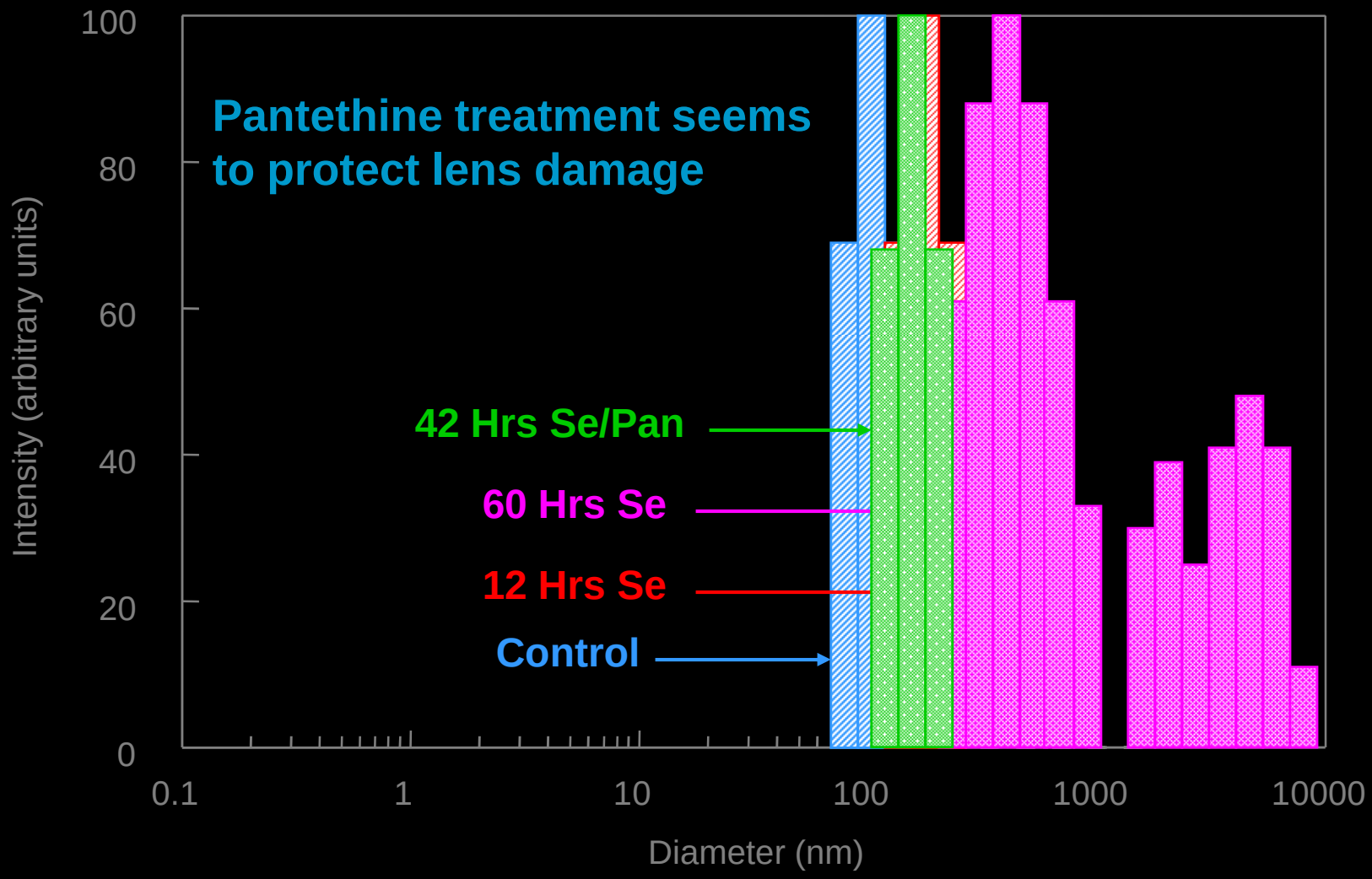
Wave-length: 670 nm

Power: 80 microwatts

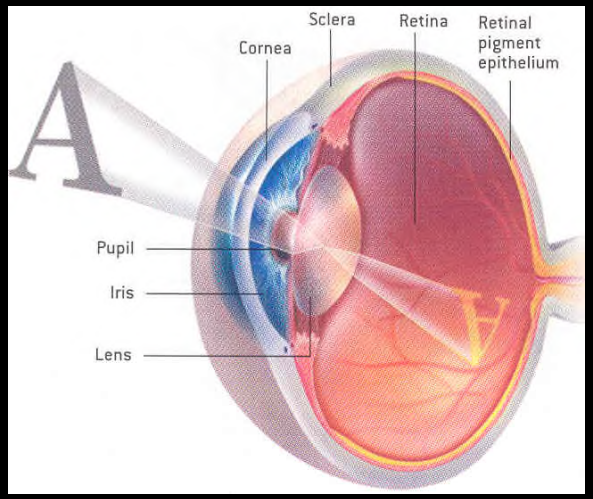
Ansari et al, Ophthalmic Tech. XIII, SPIE Vol. 4951, 2003

Pantethine Treatment in Rats

Particle-Size Distributions after DLS Exponential Sampling Analysis



Looking at Alzheimer's through the Eye



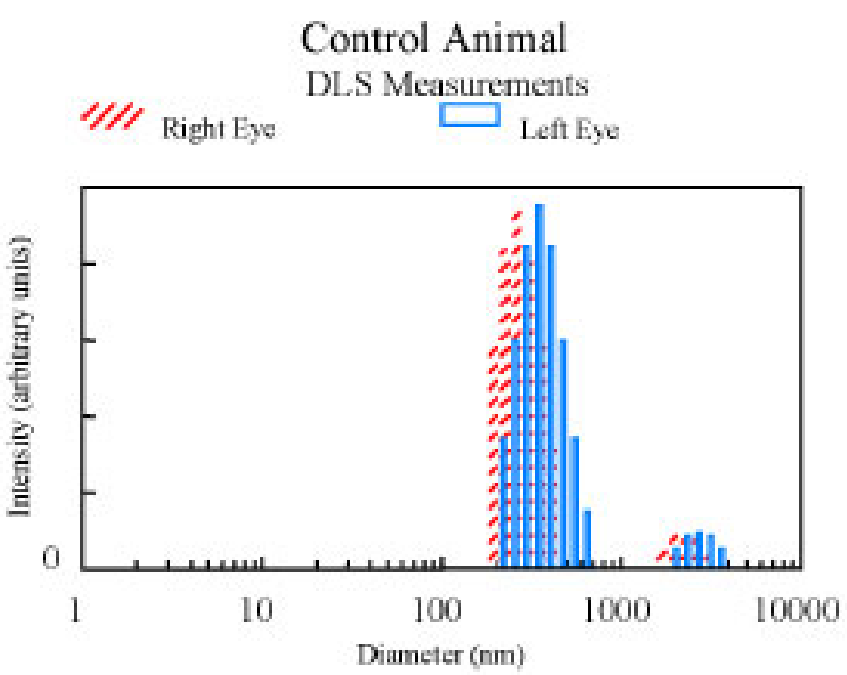
SCIENTIFIC AMERICAN

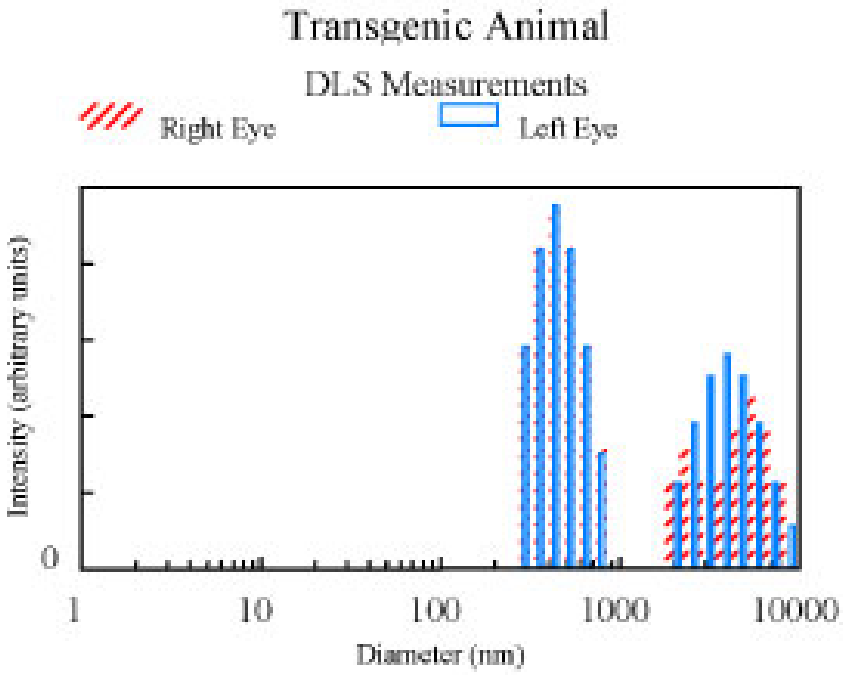
OCTOBER 2004

Studies of the lens of the eye not only could reveal ways to prevent cataracts but also might illuminate the biology of Alzheimer's, Parkinson's and other diseases in which cells commit suicide

By Ralf Dahm

Early Detection of Amyloidogenesis (Alzheimer's)





Ansari, R.R., JBO, Jan. 2004

Seeing the Invisible with DLS

Vitreous in Aging and Disease

Diabetes accelerates the Aging Process

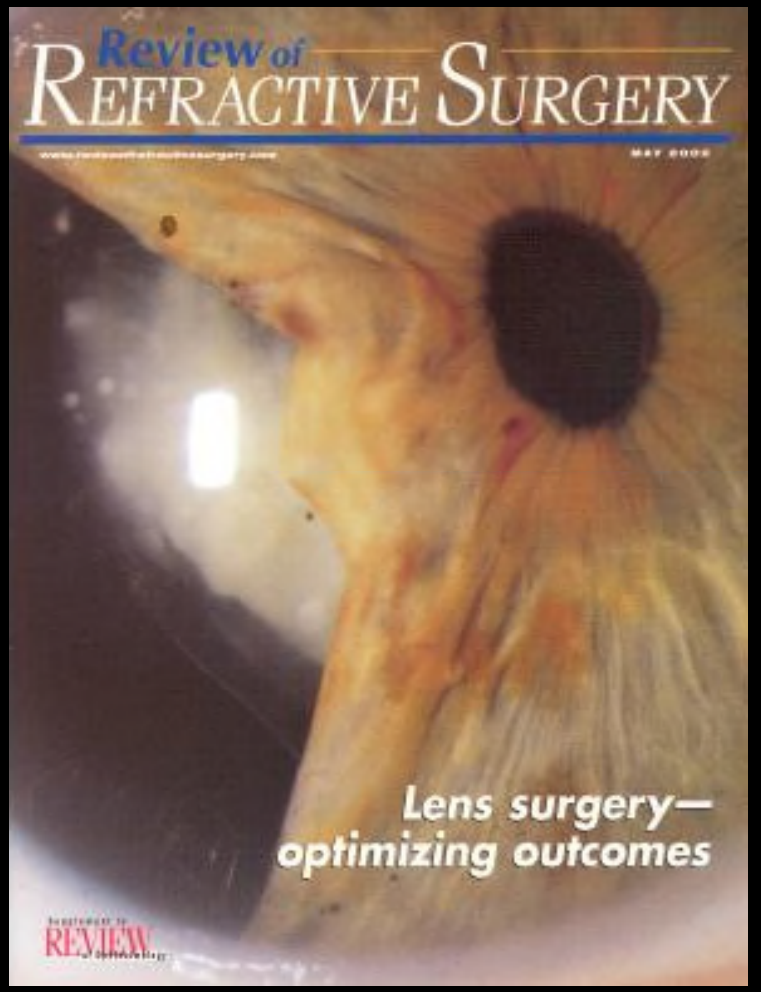
Prevention of Retinopathy of Pre-maturity

- Exp. Eye Res., 73(6), 859-866, 2001
- Graefs Arch Clin Exp. Ophthalmol, 245: 676-580, 2007

CORNEAL EVALUATION

DYNAMIC
Light Scattering
FOCUSES ON THE
Cornea

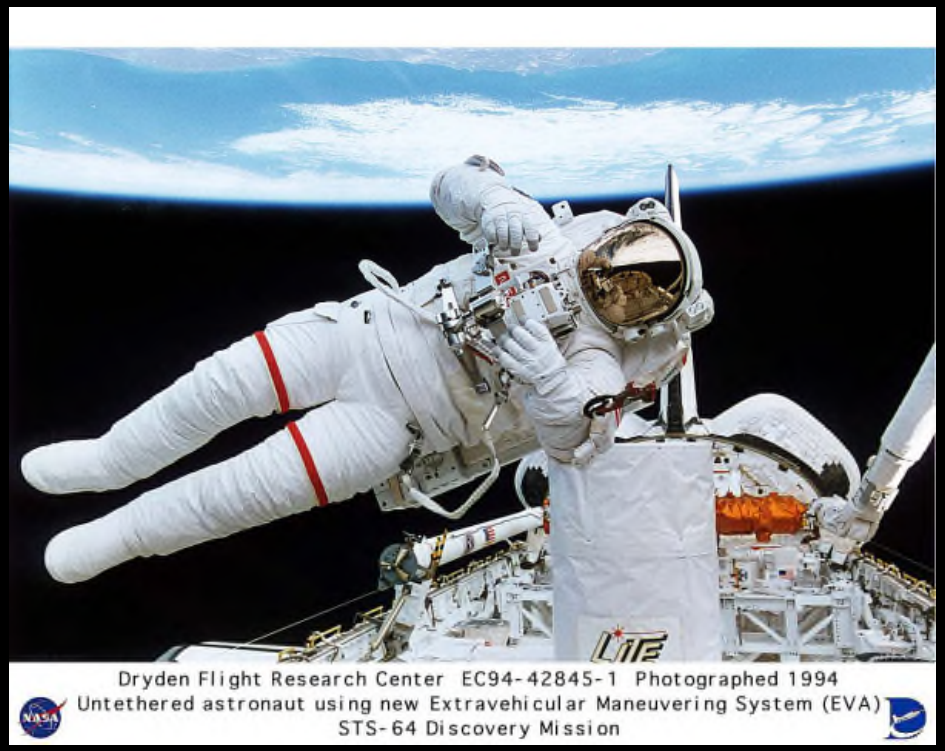
Molecular measures of clarity

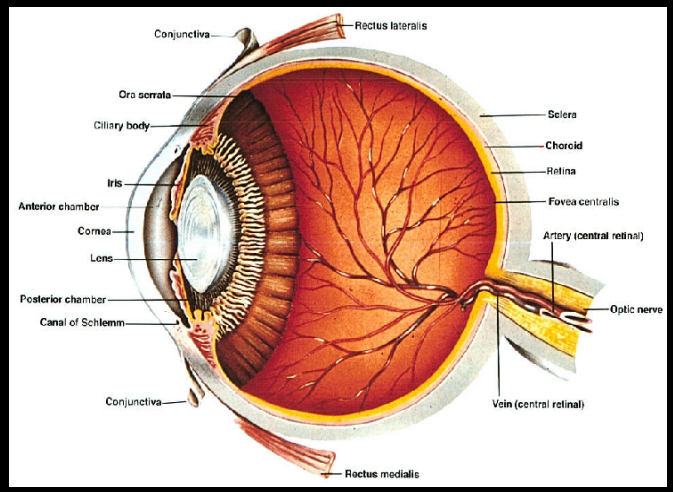


Early evaluation of Haze and
Healing post LASIK and PRK

Astronauts Report Changes in Visual Acuity and IOP in Orbital Flight

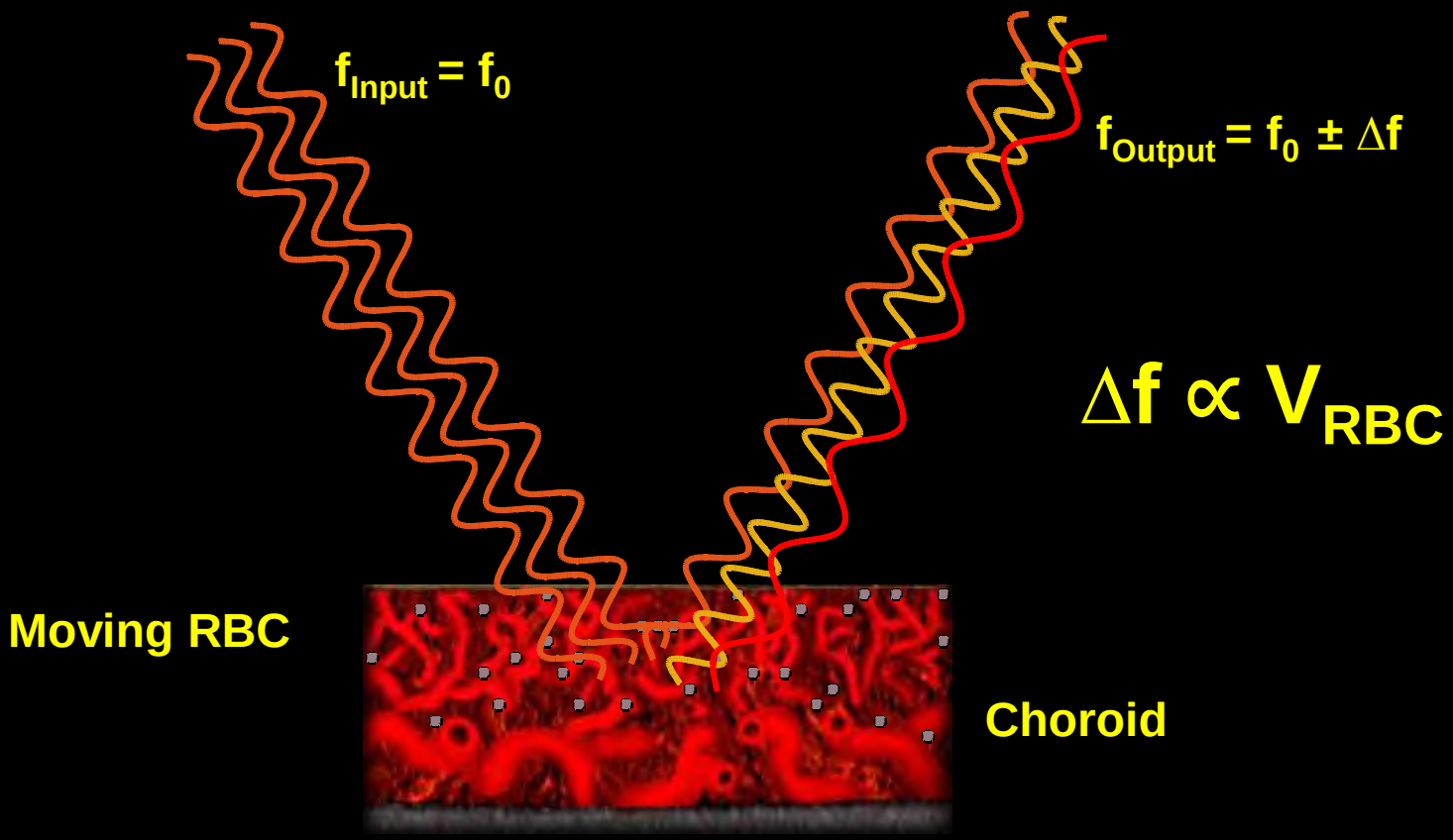
To this date this remains of unknown etiology





ChBF in response to changing fluid levels in weightless conditions

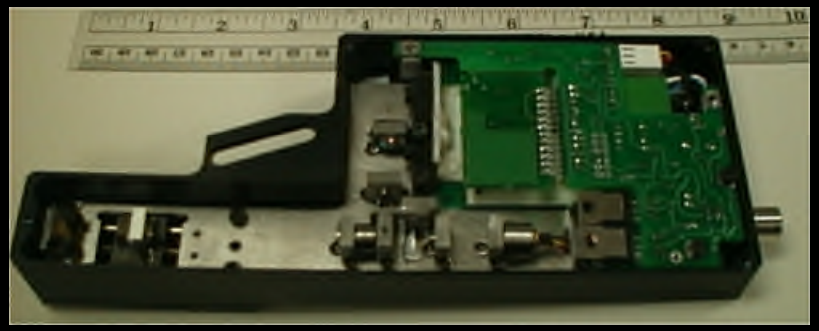
LDF Principle of Operation in Choroid



ChBF plays a major role in the supply of nutrients to the photoreceptors and pigment epithelium in humans

KC-135 Head-mounted LDF Apparatus

Weight: ~2 Lbs
Laser: 875 nm
Power: 100 μW
Duration: 10 s
Non-mydriatic

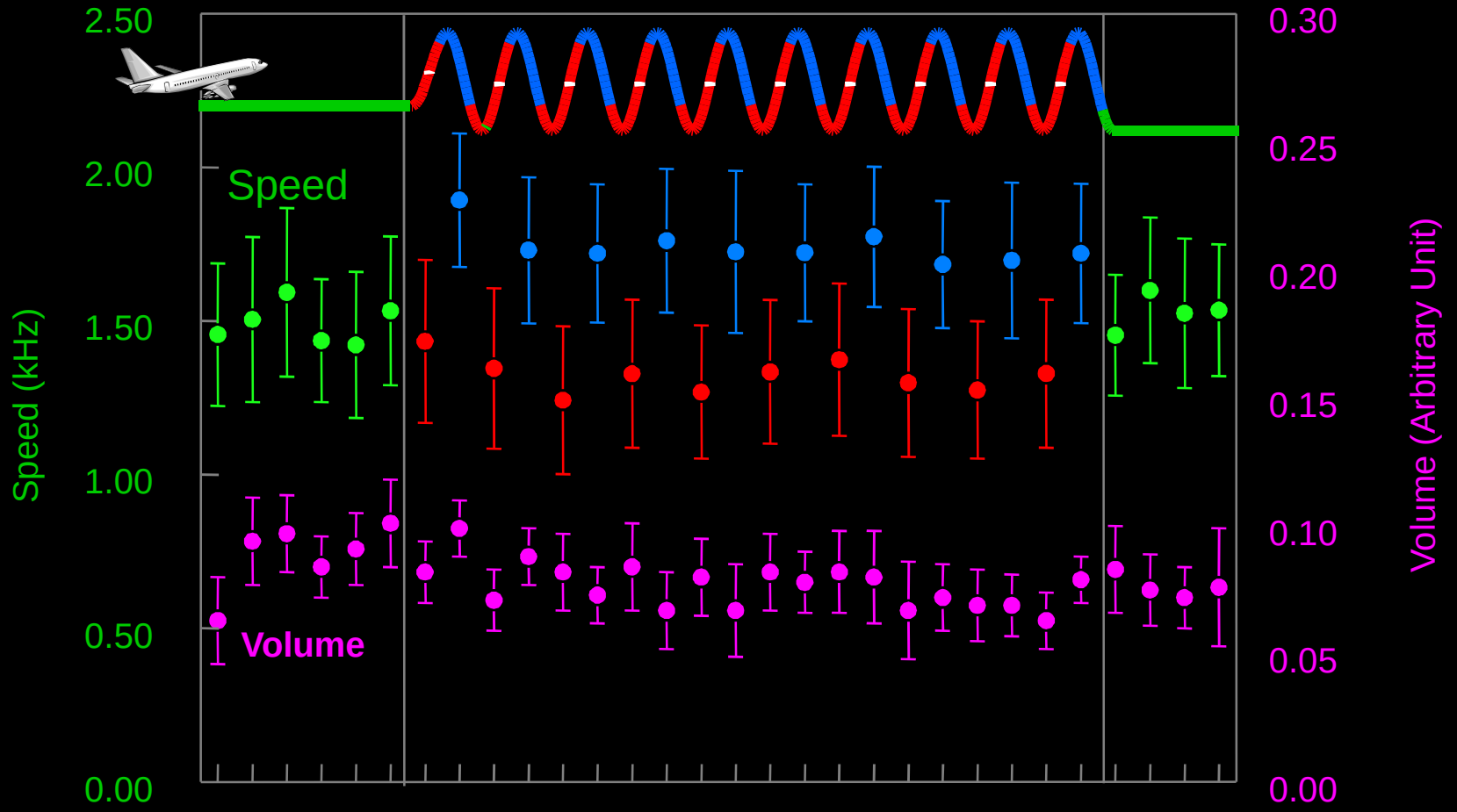


- 25 subjects studied (18 males, 7 females)
- Age: 23-51 Years old
- Subjects were allowed to blink

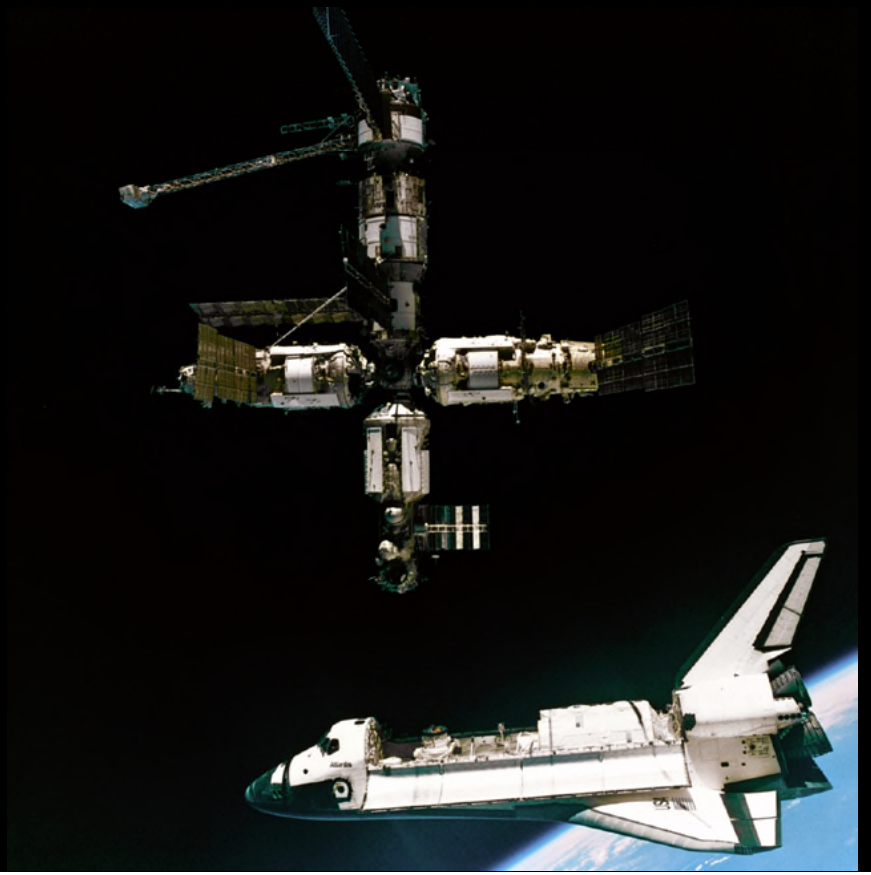
KC-135 Flight Tests

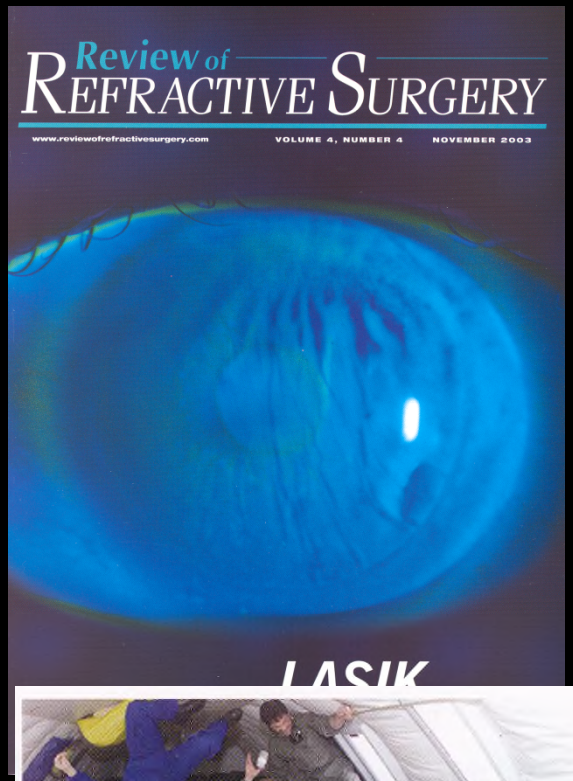
Choroidal Blood Flow Measurements in 0-G-2G

Sample Flight LDF Data: MD (49 years old)



Since there are no Baro Receptors Does the Choroid Self Regulate in Long-Duration Missions?





Microgravity Measures OF Acuity

Leslie Sabbagh, Editor in Chief

Figure 2. Blood pressure and LDF measurements in zero-g. left to right, (Upside down) Keith Manuel, (Back) Bobby Clark, King, (Front) Raul Blanco (blood pressure test subject), Ansari, and Geoffrey Iszard (LDF test subject).

Figure 1. The KC-135 microgravity airplane at NASA's Glenn Research Center in Cleveland. (left to right): Kwang Suh, (senior research associate), James King (design engineer), Rafat Ansari, (principal investigator), Ace Beall (pilot), Frank Marlow (co-pilot), John Yaniec (lead flight test director), John Lamb (flight engineer), James Withrow (flight test director).

A New Miniaturized Wireless Fiber-optic Sensor for Distal Finger-tip Injuries in Astronauts

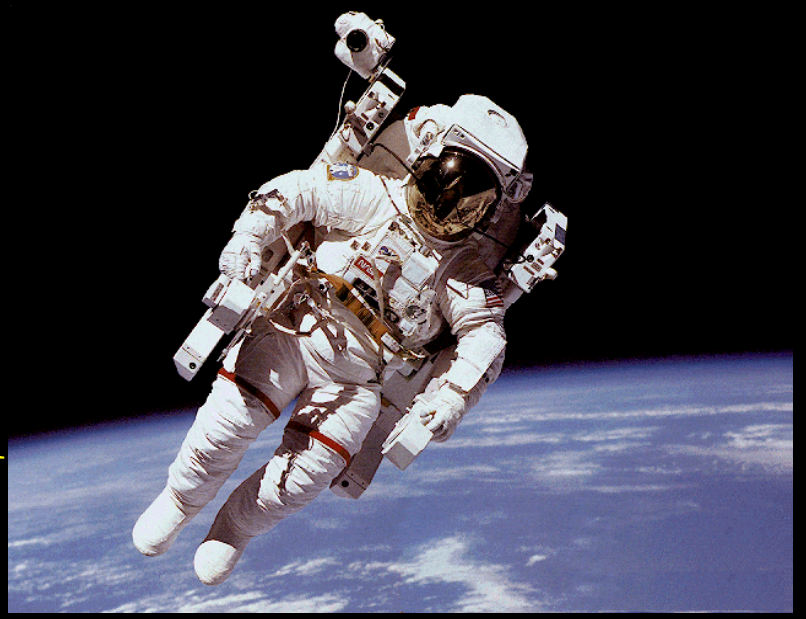
Jeffery Jones, MD, JSC

Luca Pollonini, PhD, UTHSC

Mikael Rodriguez, UTHSC

Roedolph Opperman, MIT/USRA

Jason Hochstein, ISU/USRA



EVA Physiology, Systems & Performance Project

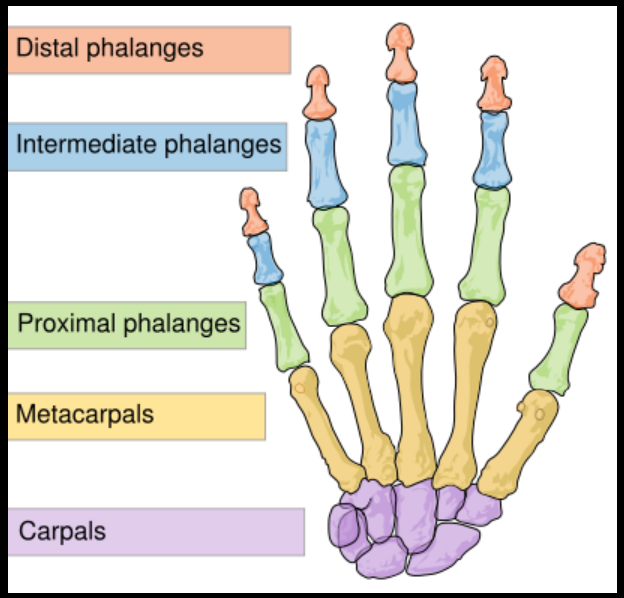
Ansari et al., Opt. Diag. and sensing, BiOS, Vol 7186-08, 2009

EMU Glove

- Most complex and most critical part of the entire suit.
- 22 Apollo-era astronauts said “of all the future improvements in the EMU suit, improving the glove is the most important”

Human Hand has 27 Bones and 25 Degrees of Freedom

In the EVA environment the hand is not only a multipurpose tool but also the primary means of locomotion, restraint, and object handling



Existing EVA gloves significantly reduce hand dexterity, range of motion, tactility, strength, and endurance. In addition, they are often uncomfortable to the point of pain and/or minor physical injury to the hands

Injuries

Fingernail delamination (onycholysis) is by far the most common injury reported among astronauts training in the NBL and performing EVA tasks.

Strauss, S. (2004). *Extravehicular mobility unit training suit symptom study report* (NASA/TP-2004-212075)

Series 4000 Astronaut Gloves (IP = 4.3 PSI)

Bladder

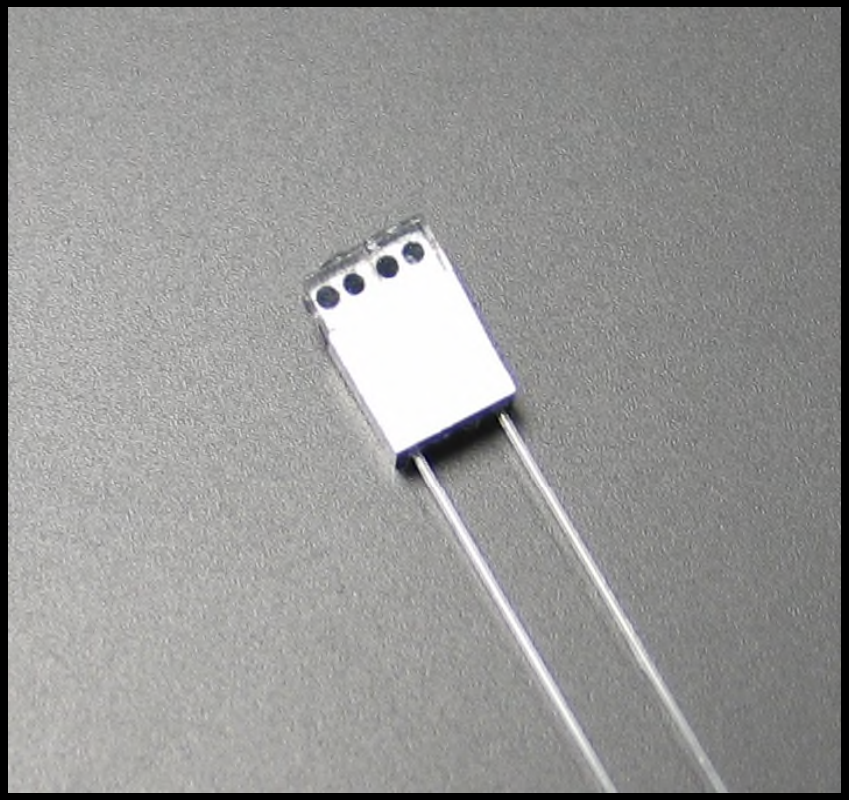
Restrainer

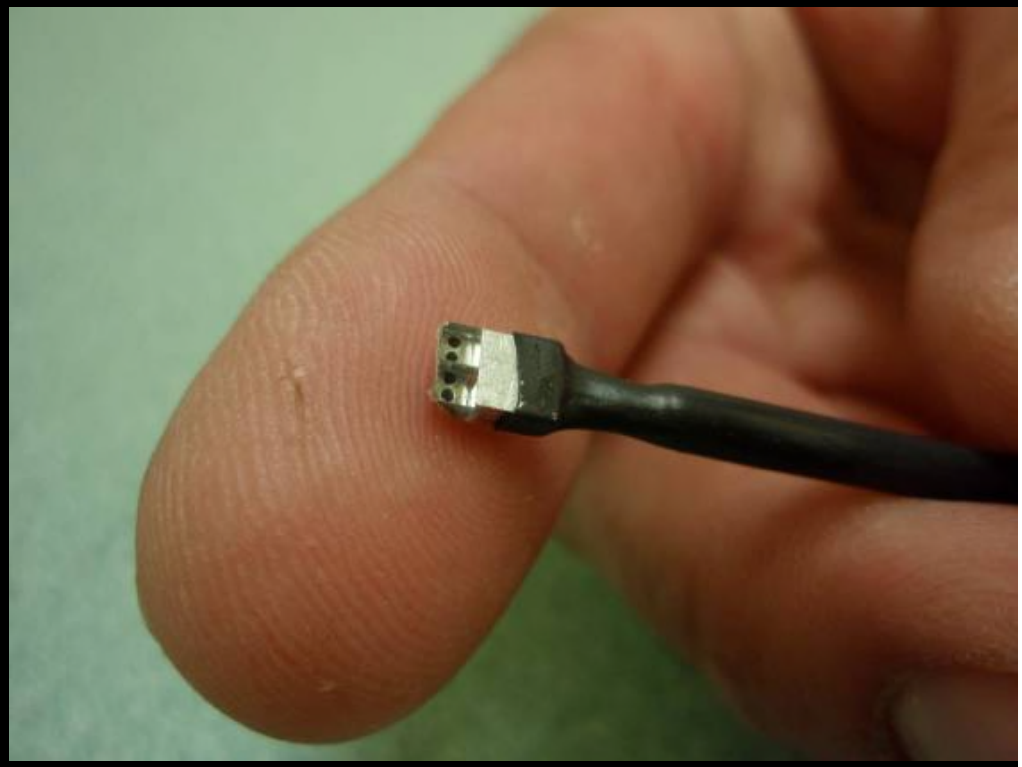
Thermal Micrometeorid Garment (TMG)

Mild Nail Injury
(nail delamination)

What are the Mechanisms of Injury to the Fingers?

New Miniaturized Sensor





2 mm x 4 mm x 6 mm embedded in the astronaut EMU glove

Pilot Study (Summer 2008)

Ansari et al., Opt. Diag. and sensing, BiOS, Vol 7186-08, 2009

- How different loading conditions influence skin blood perfusion in the finger as well as contact pressure on the hand.
- 7 subjects (6 male and 1 female) were tested
- Perfusion decrement is a probable index of damage

Proper Nutrition is Very Important because 0-G can alter absorption levels and physiologic requirements

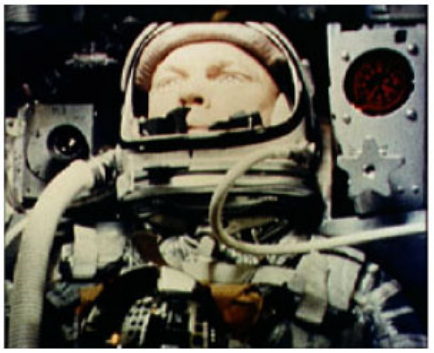
Every President should know what his astronauts are eating in space, right?

Fresh Fruit is a treat in space

Radiation Effects and Nutrition

Flashes of Light (protons/cosmic radiation ?)

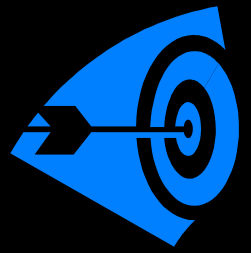
Eye is the only organ in the human body that instantly shows presence of ionizing radiation in the form of visible light sensation.



Freedom 7 Mercury 6
John Glenn
February 20, 1962

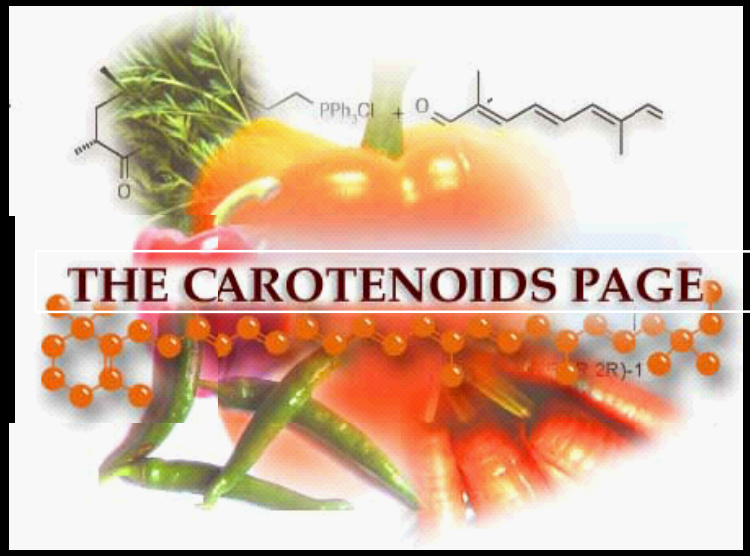
- There are no known health dangers associated with light flashes.
- But cosmic radiation in general is hazardous.
- Reactions can destroy cell nuclei and put astronauts at increased risk for AMD, cancer, and make them more susceptible to other diseases.

Diseases of radiation-exposed tissues linked to Oxidative Stress



- **Age-Related Macular Degeneration**

Association of Sunlight Exposure and Antioxidant levels with AMD (Paulus and de-Jong, Arch. Ophth. October 2008)

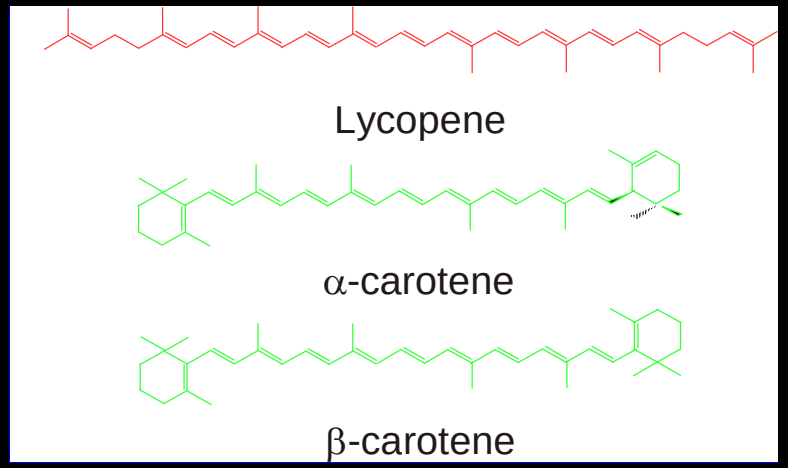


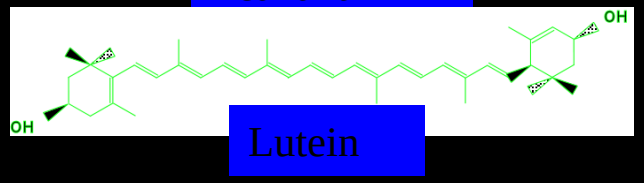
Carotenoids

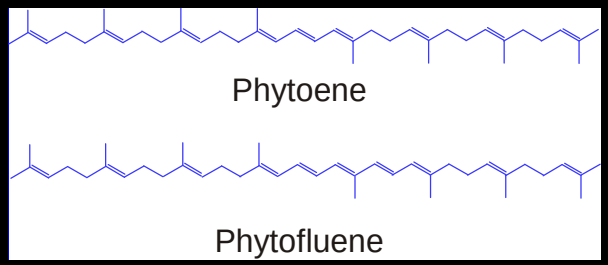
Fat-soluble antioxidants ($^1O_2$ quenchers)

Protect cellular DNA (lycopene)

Protect macular region of retina (lutein and zeaxanthin)



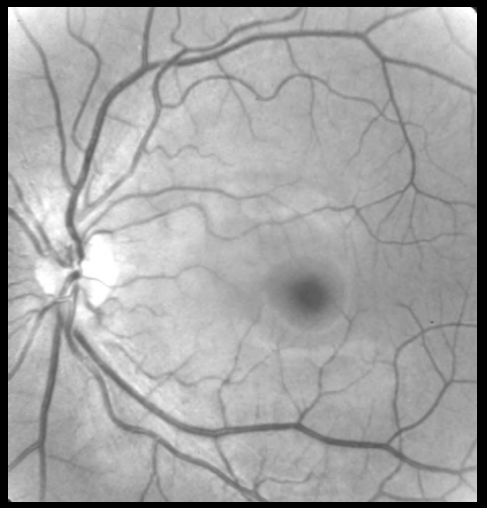




Carotenoids in the Human Retina

- Macula: retinal area of highest visual acuity
- Xanthophyll carotenoids lutein and zeaxanthin are concentrated in macula.
- Role of carotenoids: optical filtering; antioxidants (protection of macula from light-induced damage)

FILTERS

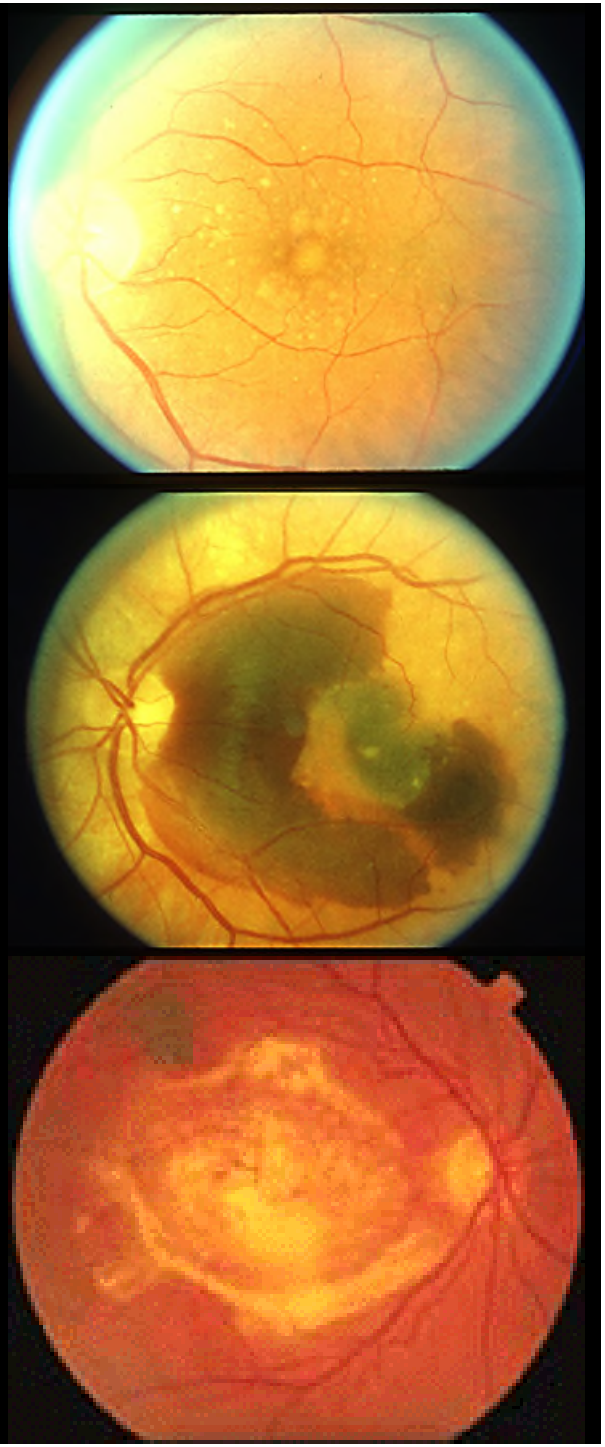


Oxidative Stress and AMD Development:

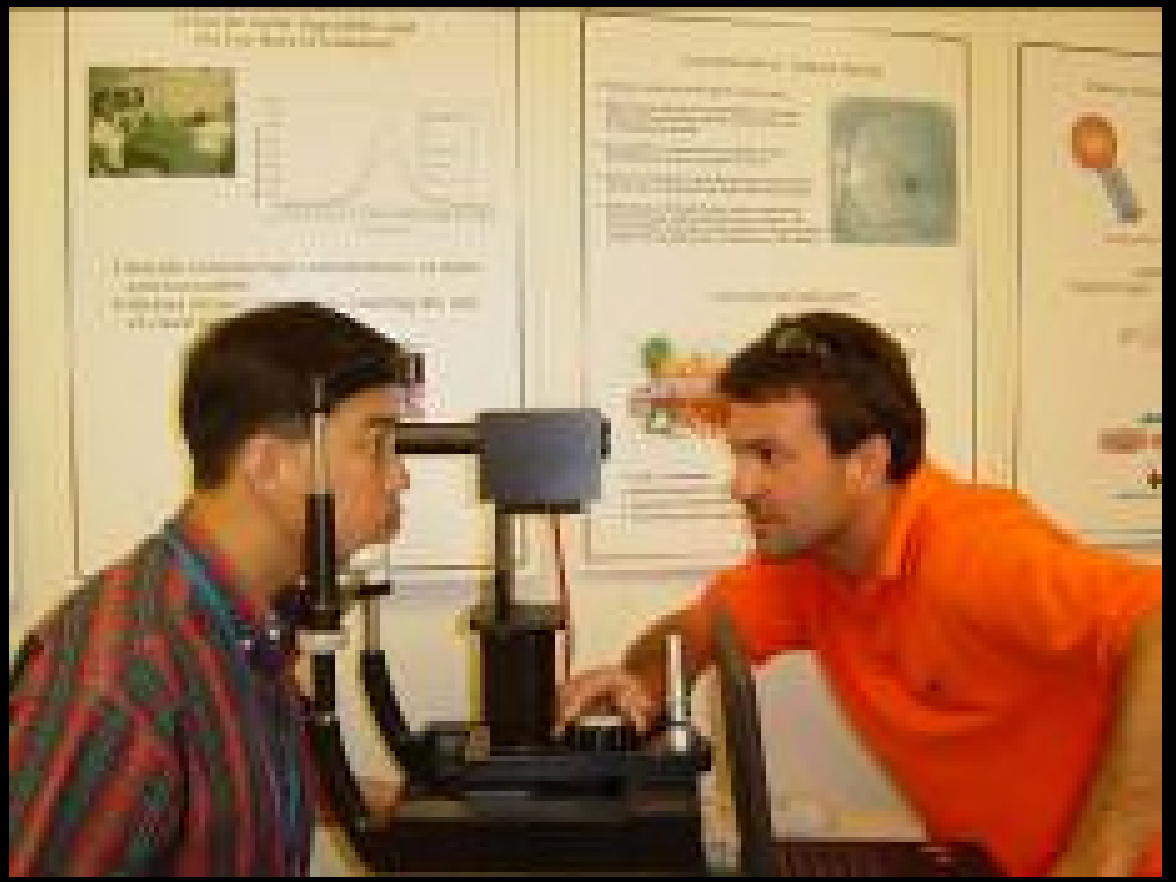
- High metabolic rate
- High blue light exposure
- High oxygen levels -ROS's
- High levels of polyunsaturated fatty acids

Pigment Changes, Formation of drusen (hard and soft), Atrophy of RPE and photoreceptors, hemorrhage, etc.

TREATMENT/COUNTERMEASURES ?

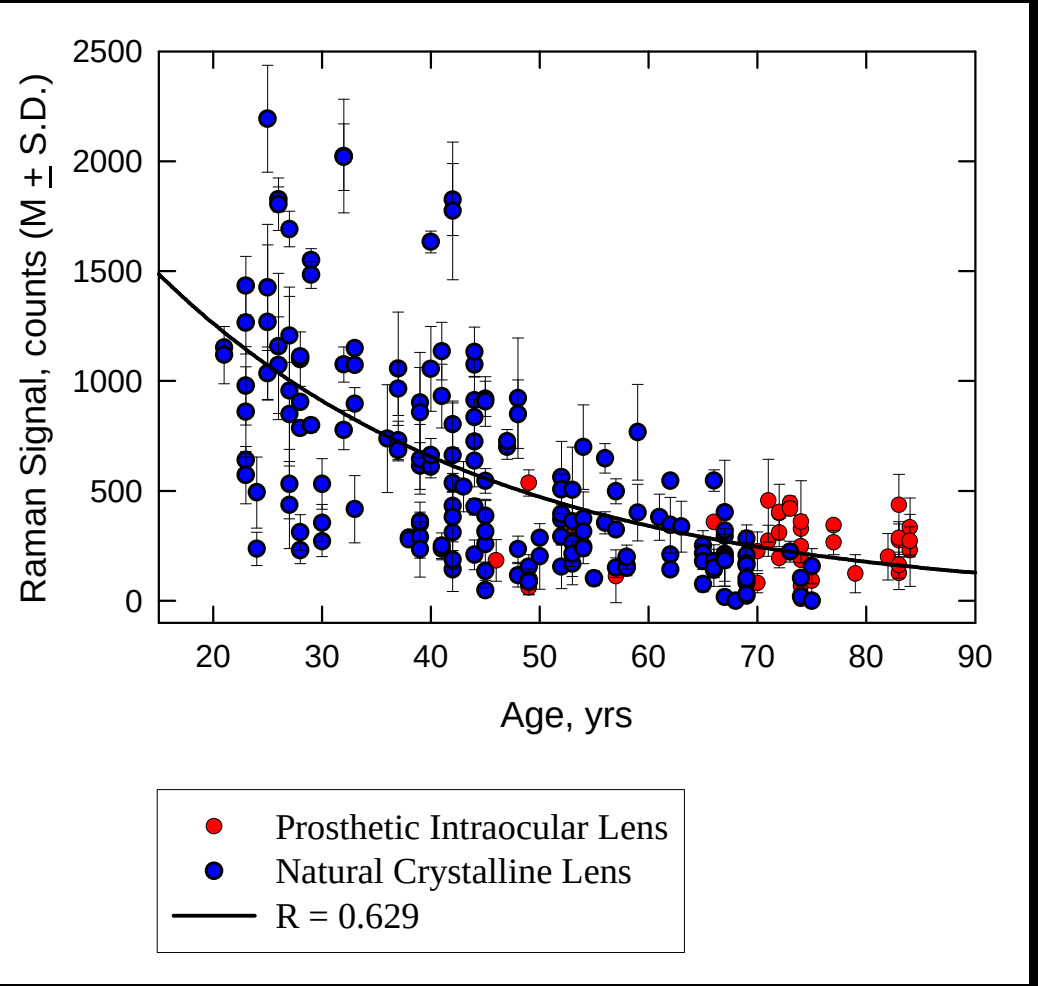


Raman Scattering in the Human Macula & Skin to Measure Carotenoids Non-Invasively

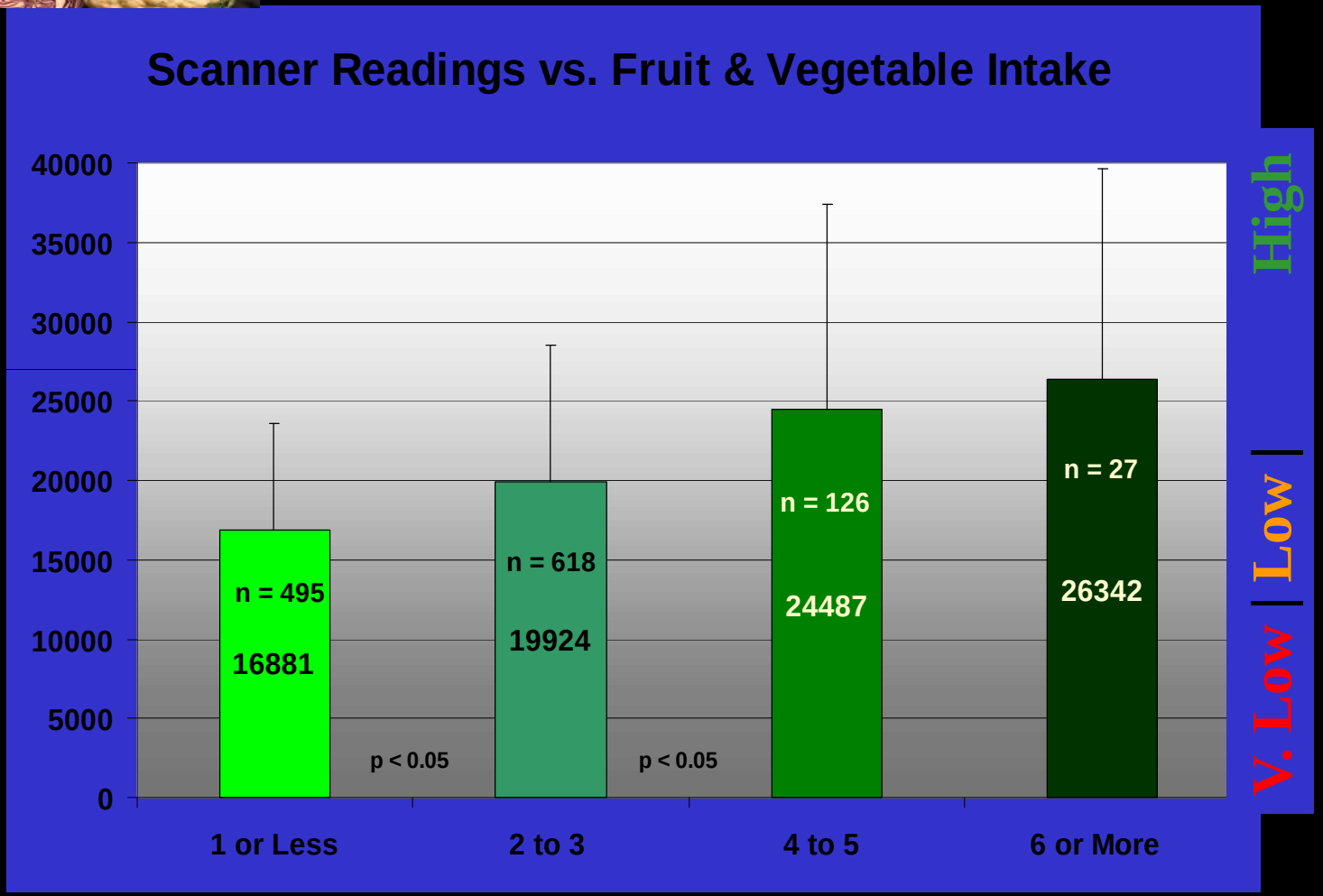


Loss of Macular Pigment with increasing Age

- Macular pigment levels were measured in 220 dilated eyes free of macular pathology or visually significant cataracts.
- Means ± standard deviation for best three out of five measurements are shown.
- *R*=0.629; *P*<0.001

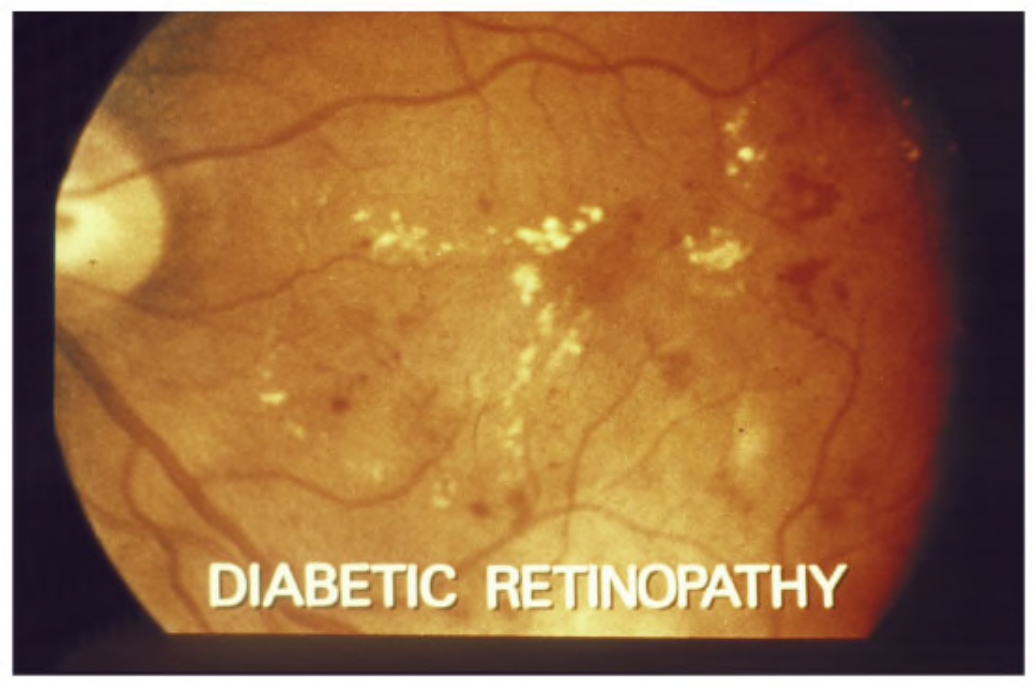


Courtesy of W. Gellerman Ph.D & P. Bernstein, MD, Ph.D. U.O. Utah



Data Courtesy of Dr. Gellerman, U.O. Utah

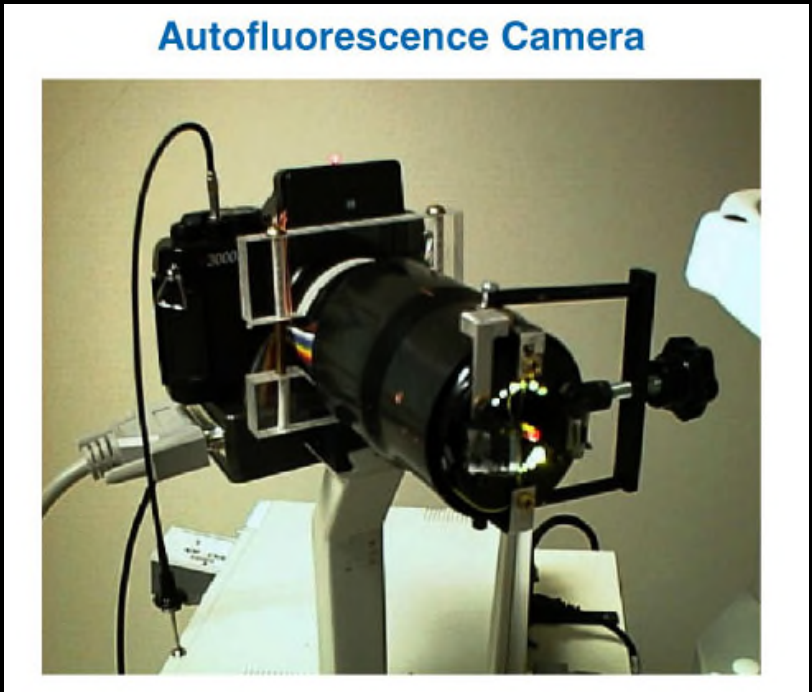
Present: Fluorescene Angiography is the Most Widely Used Technique



NON-INVASIVE AUTO FLUORESENCE MEASUREMENTS

Fundus Photo Courtesy of J. Sebag, MD, USC

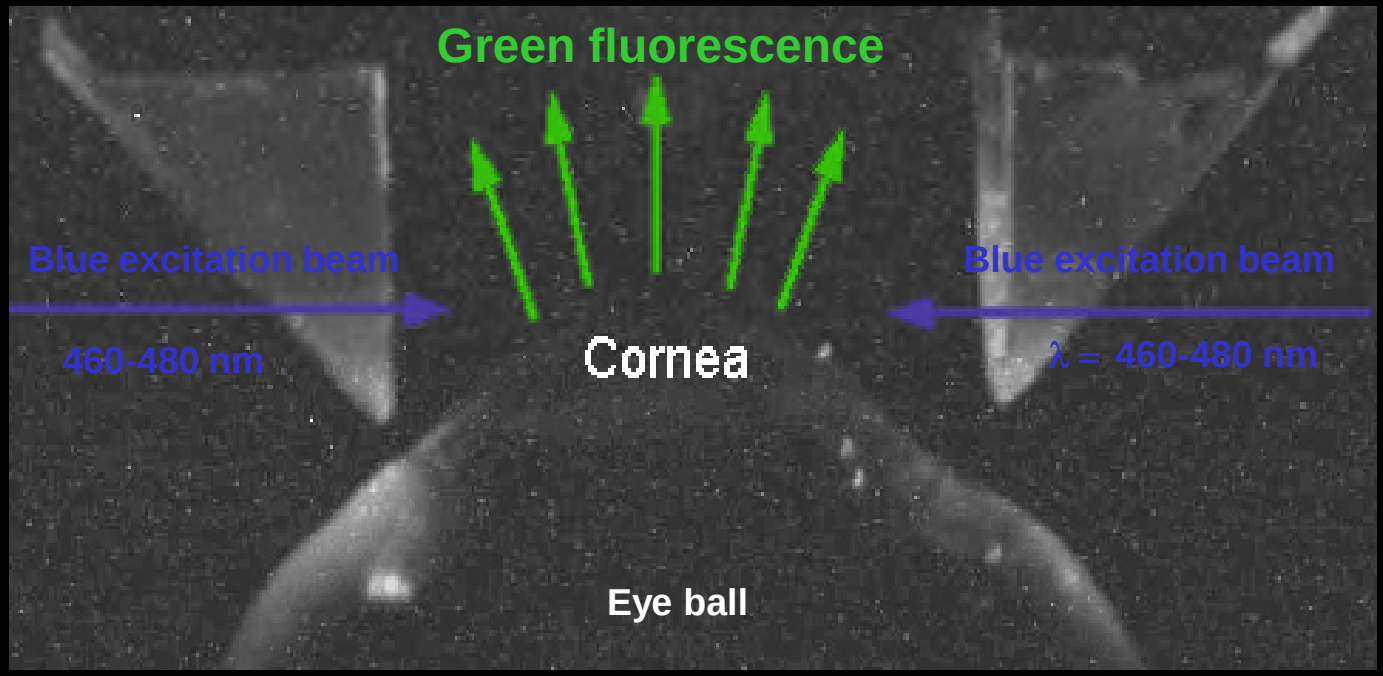
Non-Invasive Measurements of Diabetic Retinopathy through the Cornea



Metabolically active Epithelial and Endothelial cells contain fluorophores: pyridine nucleotides (NADPH) and flavins (FMN and protein-linked flavins)

Corneal Auto-Fluorescence and Diabetic Retinopathy

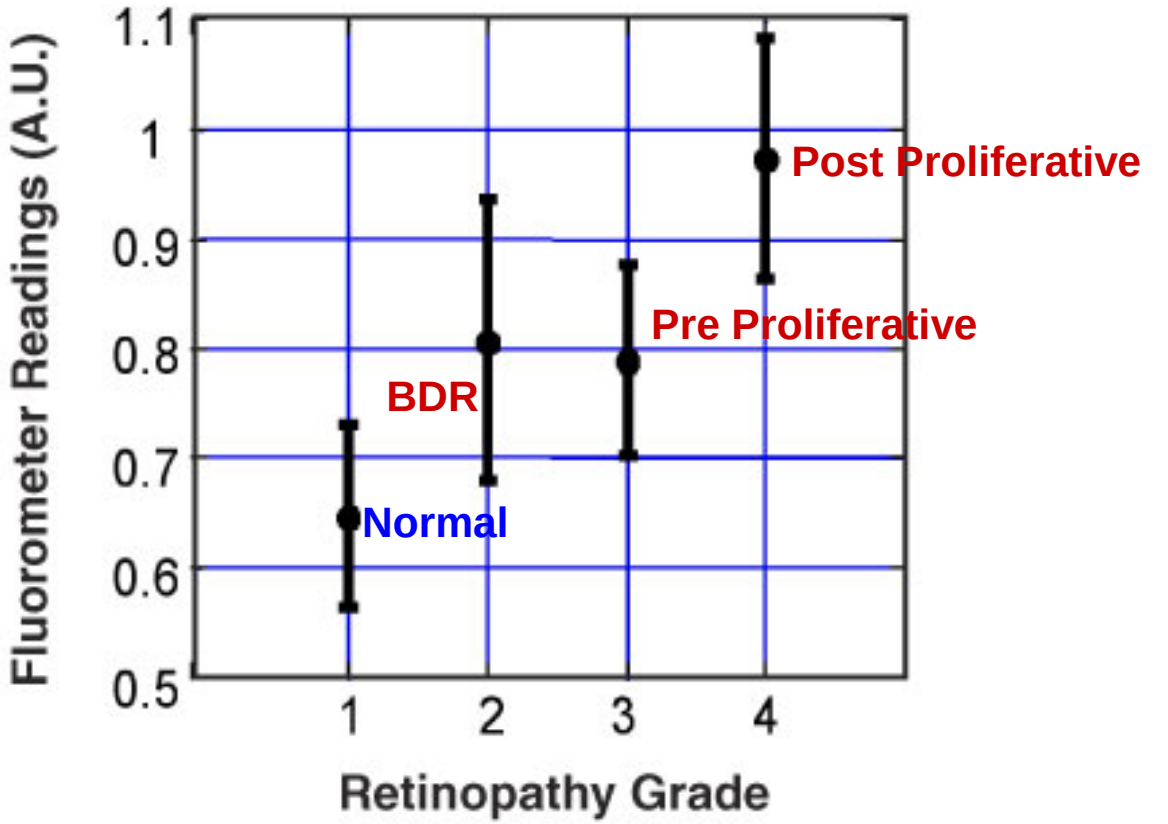
λ = 500-520 nm



NADPH fluoresce in the reduced redox state and flavins in the oxidized redox state

Results of a Preliminary Clinical Test Performed on about 90 Diabetic Subjects

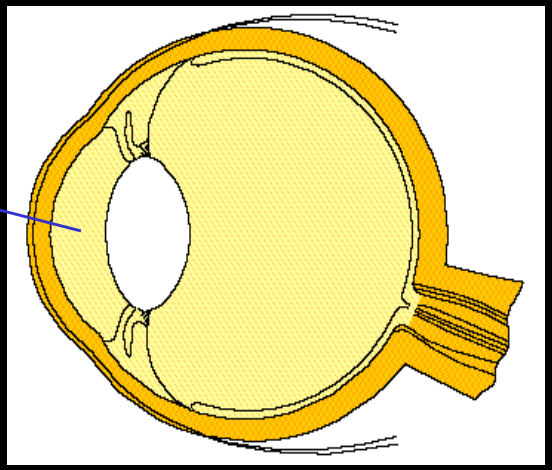
(the bars represent the standard error in the measurements)



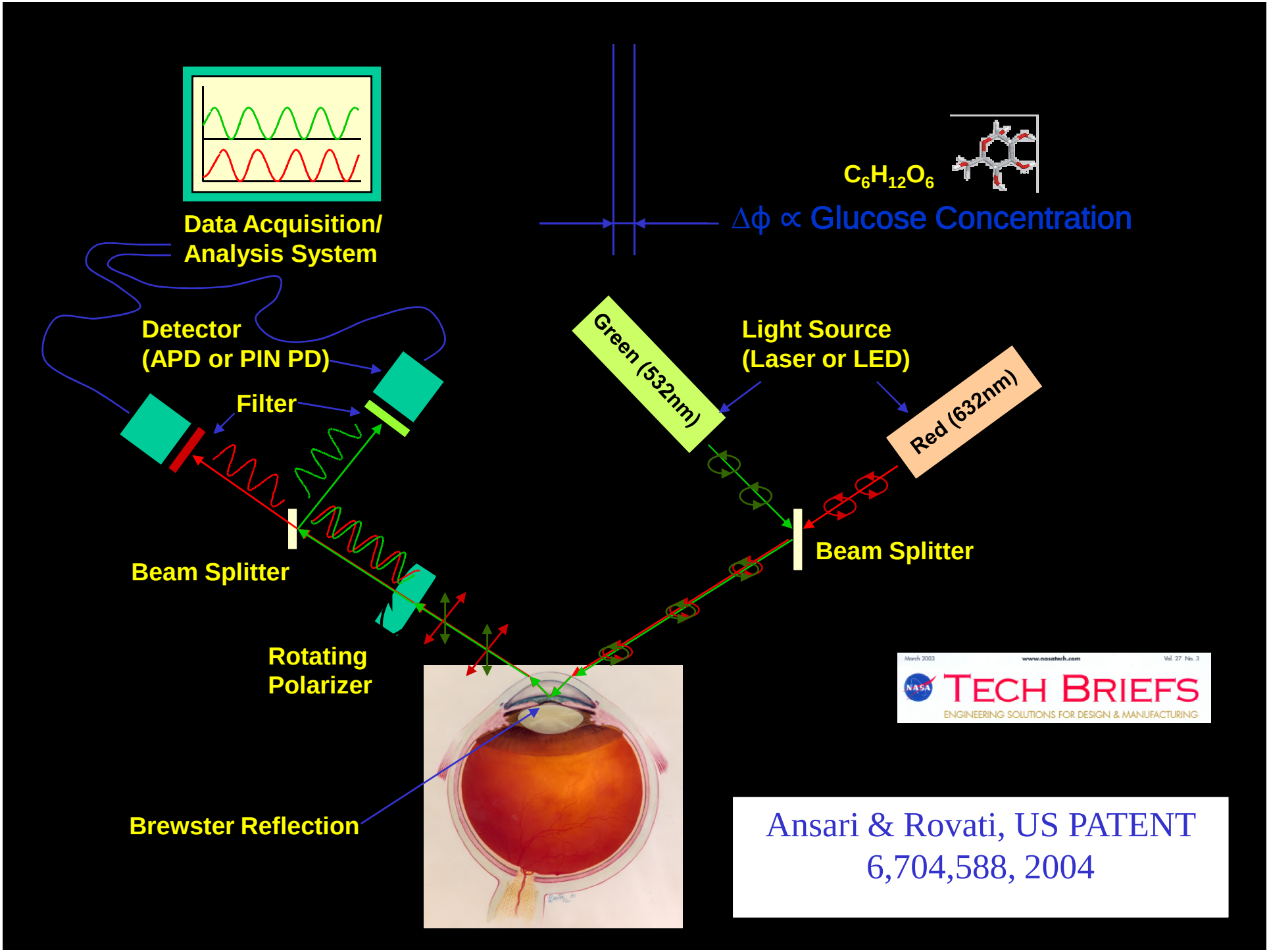
Rovati et al., J. Biomedical Opt. Vol 3, 357-363, 1999

DIABETES MANAGEMENT

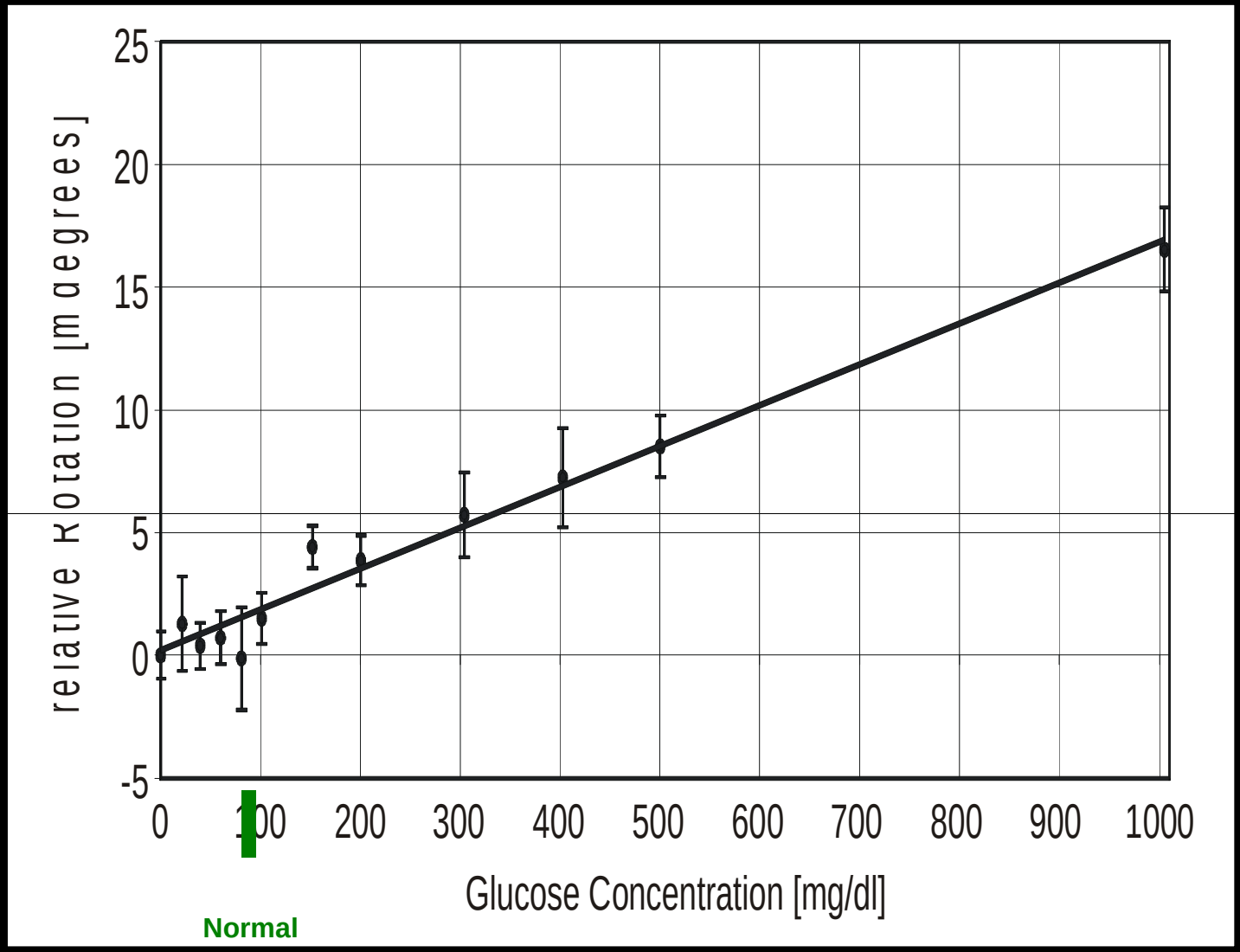
Non-invasive glucose detection:



Glucose levels in the aqueous humor reflect the blood glucose levels with a delay of only a few minutes

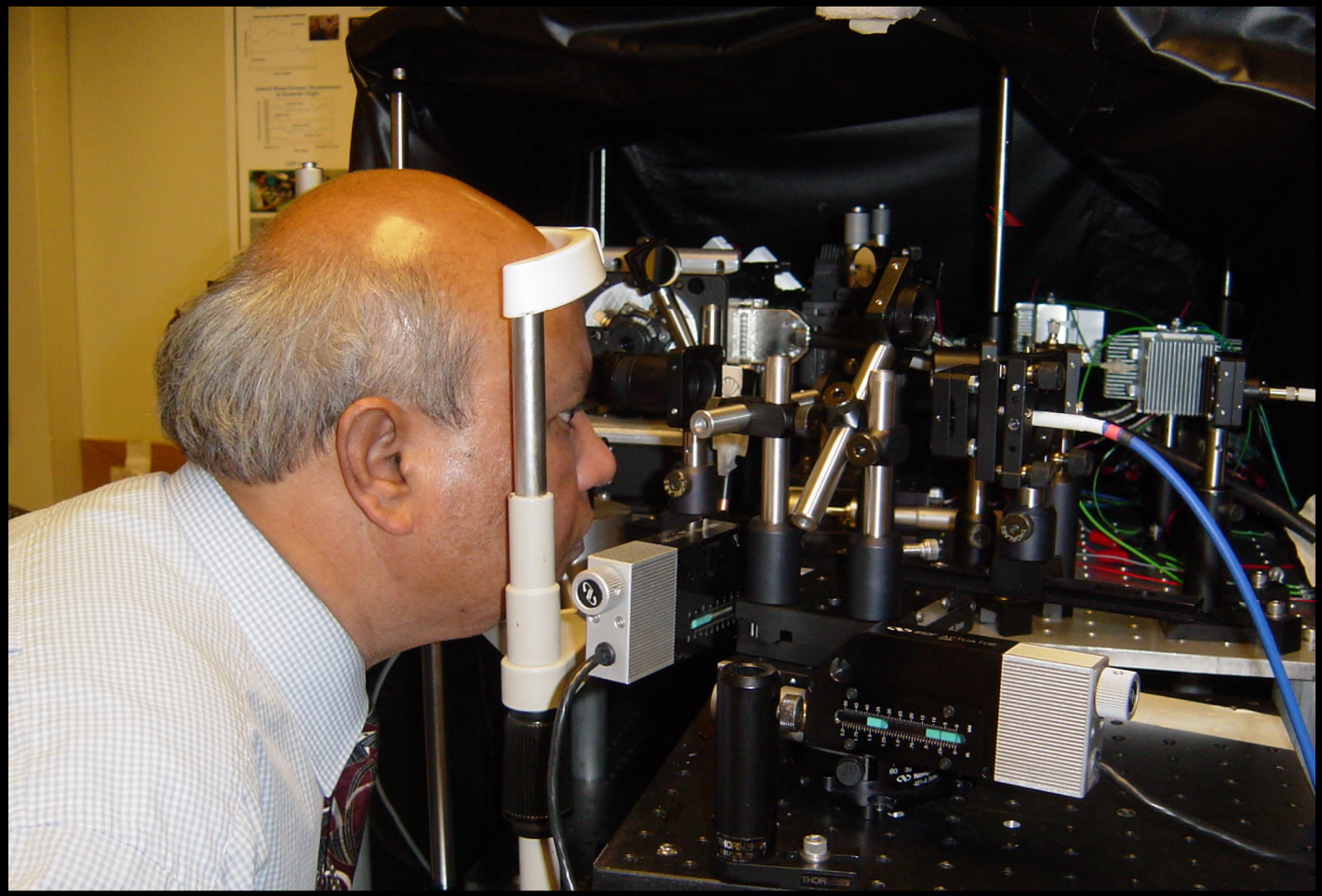

Data Acquisition/
Analysis System
$C_6H_{12}O_6$
$\Delta\phi \propto$ Glucose Concentration
Detector
(APD or PIN PD)
Filter
Green (532nm)
Light Source
(Laser or LED)
Red (632nm)
Beam Splitter
Beam Splitter
Rotating
Polarizer
Brewster Reflection
TECH BRIEFS
ENGINEERING SOLUTIONS FOR DESIGN & MANUFACTURING
Ansari & Rovati, US PATENT
6,704,588, 2004

Glucose Sensing Results



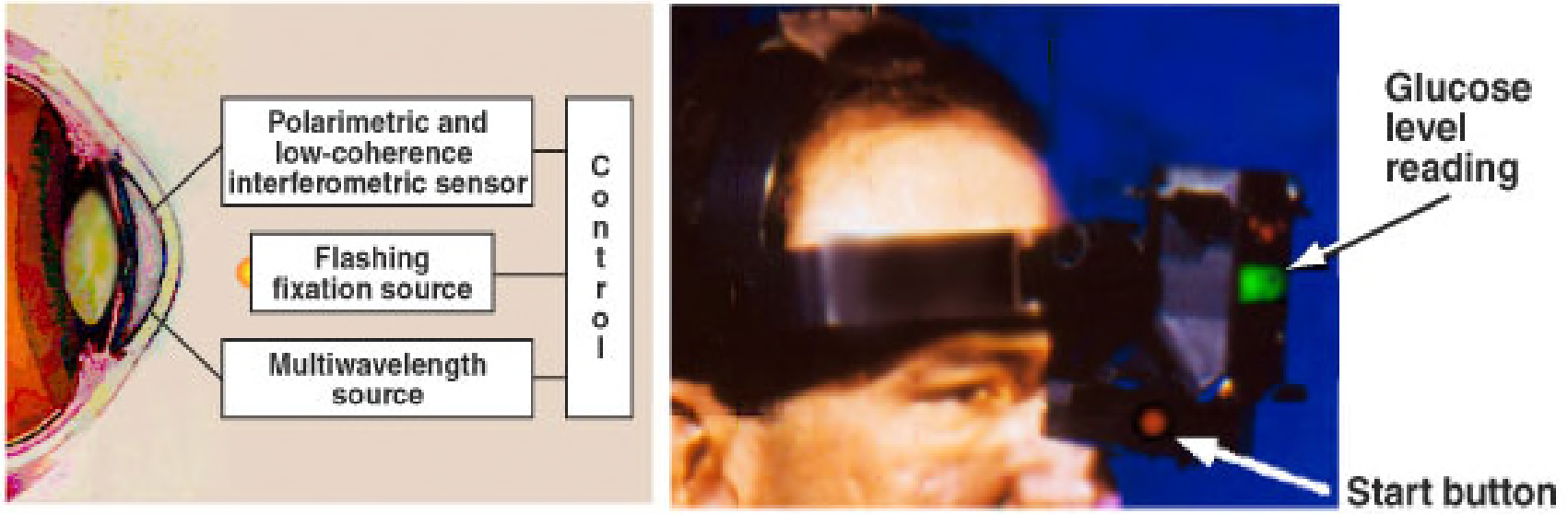
Ansari et al., JBO, Vol.9, NO. 1, (2004)

PROTOTYPE GLUCOSE SENSING INSTRUMENT



Diabetes HEALTH

April 2004



Non-Invasive Helmet-Mounted Glucose Meter

Rovati and Ansari, Handbook of Optical Sensing of Glucose in Biological Fluids and Tissues, CRC Press, 2009

Upcoming Studies

- Pre-flight/Post-flight ISS Crew
- NBL Diver Population

Changes in Oxidative Bio-markers during a mission on International Space Station

Compound Analyzed	Changes Observed in Flight
Total Anti-oxidant Capacity	Decreased 30%
SOD (super-oxide dismutase)	Decreased 10-30%
Glutathione Per-oxidase	Decreased 5-15%
Malondialdehyde	Increased 100-200%
4-OH Alkenal	Increased 50-150%
Urinary 8OHDG (urinary 8 hydroxy-2 deoxyguanosine)	Increased 40-200%

Source: Jeff Jones, MD, Flight Medicine-NASA JSC

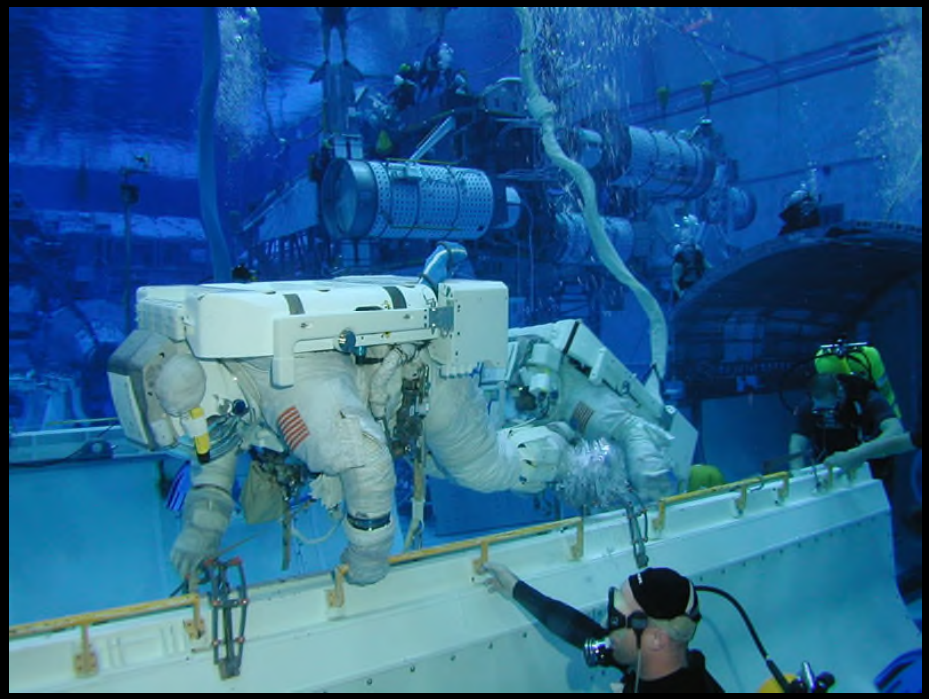
DARPA-Approved Proposal
Pre-Flight/Post-Flight Evaluations

Study of Oxidative Stress Leading to Accelerated Aging –with Non-invasive DLS and Raman Methods

- Reactive Oxygen Species (ROS)-induced final common pathways In Vivo!!
- Bio-chemical Analysis/Measure Biomarkers – Relevant to Flight
- Test Counter-measures (Anti-oxidants)

JSC CPHS APPROVAL RECEIVED, April 2009

Non-Invasive Assessment of Oxidative Stress and Possibly Accelerated Aging in NBL Diver Population Using DLS and Raman



Study to begin Soon

James S. Logan, MD

Diver Study

Unique population “at risk’ – Divers with occupational exposures to NITROX45

120 NBL Divers

Exposure Range: 0.52 Hrs-4000 Hrs

Normoxic Conditions v/s Nitrox-45

Air we breath:

78% nitrogen

21% oxygen

NBL Divers:

55% N_2

45% O_2

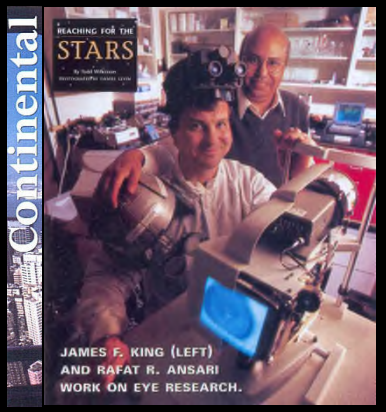
Advantage: longer no-decompression times

Disadvantage: Oxygen Toxicity

NBL Diver Pilot Study Goal

- Establish correlation between oxidative stress and repair mechanism
- Cross-sectional Study (using DLS)
- Longitudinal Study (using Raman)

Diabetes HEALTH



AMERICAN ACADEMY OF OPHTHALMOLOGY
The Eye M.D. Association

Technology Review
PUBLISHED BY MIT

CNN / WebMD

The NIH Catalyst

EyeWorld
AN INTERNATIONAL NEWSMAGAZINE FOR EYE CARE CLINICIANS
VOLUME 1, NUMBER 3 DECEMBER 1996

The New York Times

The Washington Post

HOUSTON CHRONICLE

THE PLAIN DEALER

Acknowledgments

Collaborators:

- *M. B. Datiles, MD (NIH)*
- *F. Giblin, Ph.D. (Oakland U)*
- *K. Manuel, OD (JSC)*
- *J. Logan, MD (JSC)*
- *L. Rovati, Ph.D. (U. Modena)*
- *M. Chenault, Ph.D. (FDA)*
- *N. Congdon, MD (Johns Hopkins)*
- *S. Zigler, Ph.D. (NIH)*
- *J. Sebag, MD (Doheny)*
- *W. Stark, MD (JHU)*
- *J. Clark, Ph.D. (UW)*
- *Martial Geiser (IRO)*
- *J. Jones, MD (JSC)*
- *R. Kaplan (Wake Forest)*

Co-Workers:

- *J. King (QSS)*
- *K. Suh, Ph.D. (OAI)*

Students: Drexel Univ. (PA), IRO (Swiss), and U. Modena (Italy)